Seeger, *et al.*,[11] and working up the product according to the method described above (2, method B) yielded 0.52 g (7%) of 3. It was identical with the product prepared by method A.

Permanganate Oxidation of 7-Me-AM and 7-Me-MTX. The 7-methyl compd (50 mg) was dissolved in 0.1 *N* NaOH (10 ml) and the soln was adjusted to pH 8 by the dropwise addn of 0.5 *N* HCl. $KMnO_4$ soln (5%, 1.7 ml) was added with stirring and the mixt was allowed to stand for 5 min at room temp. Excess $KMnO_4$ was destroyed by the addn of a few drops of H_2O_2 (30%) and the pptd MnO_2 was removed by centrifugation. The ppt was washed with H_2O (2 ml) and the washing and supernatant were combined and chromatographed on a column (1 × 17 cm) of DEAE-cellulose (bicarbonate form) by applying a linear gradient of NH_4HCO_3 soln (500 ml of 0.01 *M* NH_4HCO_3 in the mixing flask and 500 ml of 0.4 *M* NH_4HCO_3 in the reservoir). The pteridine fraction was identified as 2,4-diamino-7-methylpteridine-6-carboxylic acid by chromatographic and spectral comparison with an authentic sample.[8] The recovery was *ca.* 30%. The nonpteridine fractions derived from 2 and 3 possessed spectral characteristics identical with those of *p*-aminobenzoylglutamic acid and *p*-methylaminobenzoylglutamic acid, respectively.

Acknowledgments. We thank Dr. Dah Hsi Wang Ho for the enzyme assays. We are grateful to Professor Heinz Rembold for a sample of 2,4-diamino-7-methylpteridine-6-carboxylic acid.

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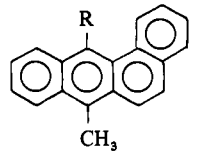
Synthesis of 5-Fluoro-6,8-dimethylbenz[*a*]anthracene

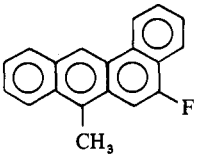
Melvin S. Newman,* Joseph H. Cecil,† and William M. Hung†

Evans Chemistry Laboratory of The Ohio State University, Columbus, Ohio 43210. *Received November 29, 1971*

Since 7-methylbenz[*a*]anthracene (1) is by far the most potent carcinogen in the monomethylbenz[*a*]anthracene series[1-3] and 5-fluoro-7-methylbenz[*a*]anthracene (2) is inactive,[4] the hypothesis has been made that deactivation of a benz[*a*]anthracene is accomplished in the host by some reaction which occurs at the 7 position if unprotected by a Me group.[5] Furthermore, it was suggested that the reaction sequence leading to cancer may occur by attack at the 5 position of 1 since 2 is without carcinogenic activity[4] whereas other fluorinated derivatives of 1 are carcinogenic.‡

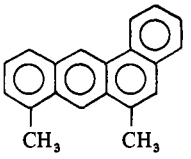


1,R = H
1a, R = CH_3

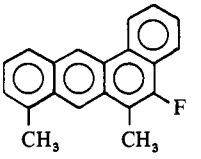


2

Support for the idea that deactivation at the 7 position is important is found in the fact that 6,8-dimethylbenz[*a*]anthracene[5] (3) is a potent carcinogen.‡,[6] In this compound deactivation at the 7 position may be blocked by 2 Me groups at 6 and 8. In order to find out if the carcinogenic activity of 3 could be eliminated by substitution of an F at 5, we have synthesized 5-fluoro-6,8-dimethylbenz[*a*]anthracene (4). Since 4 is inactive‡ it appears that the 5 position in 3 may be the position at which metabolism leading to cancer occurs, just as it appears to be in the case of 1 (and also in the case of 7,12-dimethylbenz[*a*]anthracene).‡,§



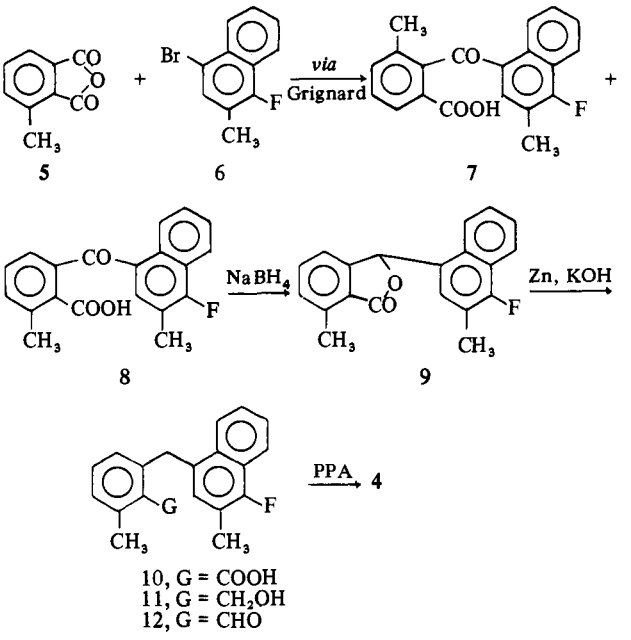
3



4

The synthesis of 4 was accomplished as outlined in Scheme I.

Scheme I



Experimental Section#

4-Bromo-1-fluoro-2-methylnaphthalene (6). 1-Amino-2-methylnaphthalene[5] was converted into 1-formylamino-2-methylnaphtha-

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‡Private communication from Drs. J. A. and E. C. Miller, McArdle Memorial Laboratory, University of Wisconsin, Madison, Wis.

§Private communication from Dr. C. B. Huggins, Ben May Laboratory for Cancer Research, University of Chicago, Ill., who reports also that 4-fluoro-, 8-fluoro-, and 11-fluoro-7,12-dimethylbenz[*a*]anthracenes produced sarcomas in over 50% of L-E rats.

#All mps are uncorrected. The term "worked up in the usual way" means that an ether–PhH extract of the organic products was washed with water, dil acid and/or base as needed, satd NaCl, and dried by filtration through a bed of anhyd $MgSO_4$. The solvent was then distd or evapd in a rotary evaporator. Nmr spectra were recorded on a Varian Associates A-60 nuclear magnetic resonance spectrometer using carbon tetrachloride as a solvent and TMS as an internal reference. Mass spectra were recorded on an Associated Electrical Industries, Ltd. MS 902 mass spectrometer.

lene,** mp 172–174° [*Anal.* ($C_{12}H_{11}NO$) C, H], in 85–90% yields by refluxing for 2.5 hr in 95% HCOOH (4 ml/g). A soln of 16 ml of Br_2 in 50 ml of $CHCl_3$ was added during 45 min to a stirred slurry of 0.6 g of Fe filings, 1.2 g of I_2, and 150 g of 1-formylamino-2-methylnaphthalene in 500 ml of $CHCl_3$. After adding 200 ml of H_2O and stirring well there was obtd 4-bromo-1-formylamino-2-methylnaphthalene,** mp 212–215°, in 76–84% yields. A pure sample,** mp 224–225° [*Anal.* ($C_{12}H_{10}BrNO$) C, H], was obtd by recrystn from Me_2CO. By hydrolysis with KOH in ethylene glycol at 100° for 2.5 hr fairly pure 1-amino-4-bromo-2-methylnaphthalene,[7] mp 78–80°, was obtd in over 90% yield. To a vigorously stirred slurry of 100 g of 1-amino-4-bromo-2-methylnaphthalene in 108 ml of concd HCl and 286 ml of H_2O cooled by a MeOH–ice bath, was added dropwise during 2 hr a soln of 15 g of $NaNO_2$ in 30 ml of H_2O.[5] After adding 60 ml of 48% HF the suspension was stirred for an addl 30 min. The solid was collected, washed with ice water, and air-dried, to yield 131.5 g (92%) of crude fluoroborate salt, mp 130.0–132.0°. The dry salt was then heated until gas evoln ceased and the residue was taken up in PhH. Evapn of the solvent followed by distn and recrystn from 2-PrOH gave 62.1 g (66%) of 6,** mp 34.5–36.5°, bp 86–90° (0.07 mm). The analytical sample was recrystd from 2-PrOH to give colorless needles, mp 38.0–38.5° [*Anal.* ($C_{11}H_8BrF$) C, H].

2-(4-Fluoro-3-methyl-1-naphthoyl)-6-methylbenzoic Acid (8). The Grignard reagent prepd in 92% yield from 55.0 g of 6 using a small amt of $BrCH_2CH_2Br$[8] in 210 ml of dry Et_2O and 30 ml of PhH was added rapidly to a hot stirred soln of 40 g of 3-methylphthalic anhydride[5] in 300 ml of PhH and 60 ml of dry Et_2O. After overnight stirring at reflux, the reaction mixt was cooled and poured onto iced HCl. The entire acid portion (52 g), isolated in the usual way, was dissolved in 600 ml of MeOH satd with HCl and refluxed overnight. The resulting ester mixt (53 g), isolated in the usual way, was treated with 700 ml of concd H_2SO_4 held at room temp. After standing 2 hr, this soln was poured on ice and sepd into acid and neutral fractions in the usual way. The crude acid 8, mp 193–203°, amounted to 33 g (44%). This material was pure enough for use in the next reaction. Pure 8,** mp 210.0–212.0° [*Anal.* ($C_{20}H_{15}FO_3$) C, H], was obtd by crystn from CH_2Cl_2–Skellysolve B with little loss. The neutral fraction obtd as described above yielded 11.3 g (15%) of the Me ester of 7.** Recrystn from MeOH gave with little loss the analytical sample, mp 169–170° [*Anal.* ($C_{21}H_{17}FO_3$) C, H].

The structure of 8 was established by decarboxylation[9] to be 4-fluoro-3-methyl-1-naphthoyl *m*-tolyl ketone (**8a**) which was identical with an authentic sample prepared by reaction of 4-fluoro-3-methyl-1-naphthylmagnesium bromide with *m*-tolunitrile. As the ketone is a liquid, the 2,4-dinitrophenylhydrazones (C, H, N), mp 228.0–230.0° dec** [*Anal.* ($C_{25}H_{19}FN_4O_4$) C, H, N] (alone and mixed), were prepd and compared. The ir spectra were identical.

7-Methyl-3-(4-fluoro-3-methyl-1-naphthyl)phthalide (9). Attempted Zn reductions of 8 under alk and acid conditions resulted in loss of F. Accordingly 8 was reduced to 9 in 86% yield (based on 8 consumed) essentially as described for the prepn of 3-phenylphthalide.[10] Recrystn from Skellysolve B gave the analytical sample of 9,** mp 162.0–162.5° [*Anal.* ($C_{20}H_{15}FO_2$) C, H, F].

2-(4-Fluoro-3-methyl-1-naphthylmethyl)-6-methylbenzoic Acid (10). To a hot soln of 9.8 g of 9 in 10% KOH–ethylene glycol was added 30 g of Zn activated by a trace of $CuSO_4$. The suspension was refluxed overnight, cooled, and filtered. The filtrate was worked up in the usual way to yield 1.4 g of recovered lactone and 7.2 g (85%) of 10, mp 171–174°. Recrystn from 60–110 petr ether–PhH gave the analytical sample of 10,** mp 173.0–174.0° [*Anal.* ($C_{20}H_{17}FO_2$) C, H, F].

5-Fluoro-6,8-dimethylbenz[*a*]anthracene (4). Attempts to cyclize 10 and to reduce the resulting benzanthrone failed to yield 4. The redn of 10 with LAH in Et_2O and in THF gave mixts of aldehyde 12 and alcohol 11 in about 70% yield. When these mixts were oxidized wtih CrO_3 in pyridine at room temp for 2 hr, crude oily 12 was obtained. This material was then heated with PPA on a steam bath for 15 min. The product isolated in the usual way was treated with picric acid in EtOH. Recrystn from EtOH afforded dark red elongated prisms of the picrate** of 4, mp 147.5–148.0° [*Anal.* ($C_{26}H_{18}FN_3O_7$) C, H, N]. By chromatog on alumina, followed by recrystn from PhH–EtOH, 4** was obtd (in 62% overall yield from the crude mixt of 11 and 12) as pale yellow prisms, mp 125–126° [*Anal.* ($C_{20}H_{15}F$) C, H, F].

**All compounds designated by a double asterisk had analyses by Galbraith Labs, Knoxville, Tenn., within ±0.02% of theory for the elements listed in parentheses.

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New Compounds

2-Pyrazinecarboxanilides

Walter L. McKenzie

Astra Pharmaceutical Products, Inc., Worcester, Massachusetts 01606

and William O. Foye*

Department of Chemistry, Massachusetts College of Pharmacy, Boston, Massachusetts 02115.

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A number of pyrazinamides have been prepared and evaluated for their tuberculostatic[1,2] and local anesthetic activity.[3] Pyrazinecarboxanilides, however, have not been reported, and it was desired to obtain the anilide, 2-toluidide, 2,6-xylidide, and 2,4,6-mesidide both as intermediates for the preparation of the corresponding piperazinecarboxanilides[4] and for evaluation as local anesthetics. The pyrazinecarboxanilides were obtained and subjected to primary screening for biological activity.[5] Neither local anesthetic nor any significant biological effect was found with these compounds.

Experimental Section

Two methods were utilized in their synthesis. Method I, a modification of that of Solomons and Spoerri,[3] involved the prepn of 2-pyrazinoyl chloride using $SOCl_2$ in the absence of the arom amine. In method II, a modification of that of Lemaire *et al.*,[6] the acid chloride was prepd in the presence of the amine using PCl_3. Equiv yields were obtd from the 2 procedures, but method II was less time consuming.

All melting points were detd with a Mel-Temp apparatus and are uncor. Ir spectra were obtd with a Perkin-Elmer 137B spectrometer. Microanalyses were done by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Where analyses are indicated by symbols of the elements, analytical results were within ±0.4% of theoretical values.