Synthetic Studies on Potential Metabolites of Carcinogenic Aza Aromatic Hydrocarbons. Part II. Non-K-Region Oxidised and Reduced Derivatives of 7-Methylbenz[*c*]acridine

Bui Vinh Lap, L. J. Boux, H. T. A. Cheung and G. M. Holder*

Department of Pharmacy, University of Sydney, Sydney, N.S.W., 2006 Australia

Received April 8, 1982

Two phenolic derivatives of the weakly carcinogenic aza aromatic hydrocarbon 7-methylbenz[*c*]acridine were prepared as reference compounds for studies of the mammalian metabolism of the carcinogen. Also, 1,2,3,4- and 8,9,10,11-tetrahydro-7-methylbenz[*c*]acridine were made as intermediates for synthetic studies directed toward preparation of dihydrodiols of 7-methylbenz[*c*]acridine.

J. Heterocyclic Chem., **20**, 281 (1983).

The carcinogenic aza aromatic compound 7-methylbenz[*c*]acridine (**1**) (1) is the subject of current metabolism and metabolite activation studies directed toward identifying those metabolic products which lead to reactive alkylating agents (2). Comparisons with polycyclic aromatic hydrocarbons suggest that certain dihydrodiol derivatives are candidates for those metabolic products (3).

The previous paper in this series (4) described the synthesis of a number of K-region derivatives of 7-methylbenz[*c*]acridine (**1**), some of which have been shown to be metabolites of (**1**) formed in liver preparations (2). In this paper, we report the synthesis of two phenols, *viz.* 9- and 11-hydroxy-7-methylbenz[*c*]acridine (**2** and **3**), and on synthetic approaches to potential metabolites with non-aromatic A- or D-rings.

For the preparation of 9- and 11-hydroxy-7-methylbenz-[*c*]acridine we used the reaction between an *N*-aryl-1-napthylamine and acetic anhydride catalysed by zinc chloride, *viz.* the modified Bernthsen reaction (5). Starting with *N*-(*p*-methoxyphenyl)-1-napthylamine (**4**) (6) and *N*-(*o*-methoxyphenyl)-1-napthylamine (**5**) (6), this reaction proceeded with concurrent cleavage of methyl ether groups yielding the required 9- and 11-hydroxy-7-methylbenz[*c*]acridines (**2**) and (**3**) respectively. The identity of the two phenols was suppported by the ^{1}H nmr data (Table 1). Thus, each shows the characteristic downfield signal (δ 9.3) for H-1 at the bay-region, and the splitting pattern and chemical shifts of the protons in ring D are compatible with the location of the hydroxyl group as predicted by the chosen starting materials (See Table 1).

While the K-region derivatives of 7-methylbenz[*c*]acridine are conveniently obtained *via* epoxidation of the electron-rich 5,6-double bond (4), synthetic approaches to the non-K-region A- and D-ring derivatives (other than simple phenols) require the construction of the appropriate perhydro-ring. A simple approach is by reduction of 7-methylbenz[*c*]acridine (**1**), and this was successful for the preparation of 8,9,10,11-tetrahydro-7-methylbenz-[*c*]acridine (**6**). Thus hydrogenation of **1** in trifluoroacetic acid over Adams catalyst gave the D-ring tetrahydro-compound **6** in 27% yield. The product **6** has the appropriate molecular weight by mass spectral analysis (electron-impact and methane chemical-ionization), and the position of saturation was clearly shown by the retention of the characteristic signal of the bay-region proton H-1 in ring A (resonating at the downfield position of δ 9.3 due to anisotropic and steric effects). Signals for four non-aromatic D-ring protons appear at δ 1.8-2.0 (H-9 and H-10), 2.7 and 3.2 (benzylic protons at 8 and 11). As the

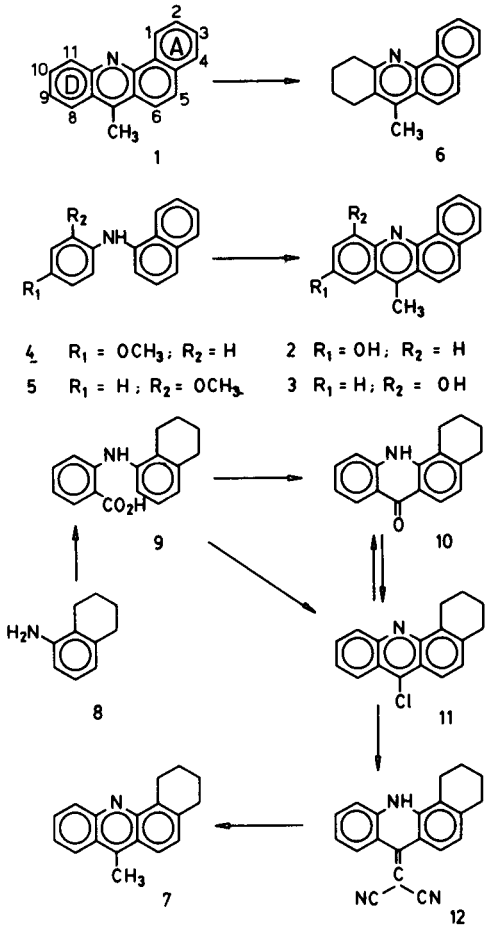

Table 1

^{1}H NMR Data (a)

Proton	**2** (b)	**3** (b)	**6**	**7**	**10**	**11** (c)	**12**
1	9.4 m (d)	9.3 m (d)	9.3 m (d)	3.45 m	2.7-2.9 m	3.35 m	2.8-3.0 m
4	7.65-7.95 m	7.6-7.8 m		2.9 m		2.85 m	
2 & 3				1.9-2.0 m	1.7-2.05 m	1.8-2.0 m	1.8-2.1 m
5	7.8 d (e,f) ($J_{5,6}$ 9.2)	7.55 d (e,f) ($J_{5,6}$ 9.2)	7.5-7.9 m	7.05 d ($J_{5,6}$ 9.0)	7.0 d ($J_{5,6}$ 8.7)	7.15 d ($J_{5,6}$ 9.0)	7.05 ($J_{5,6}$ 8.7)
6	8.1 d ($J_{5,6}$ 9.2)	7.85 d ($J_{5,6}$ 9.2)		7.85 d ($J_{5,6}$ 9.0)	8.25 d ($J_{5,6}$ 8.7)	8.0 d ($J_{5,6}$ 9.0)	8.4 d ($J_{5,6}$ 8.7)
8	7.5 (e)	7.6 dd ($J_{8,9}$ 8.8, $J_{8,10}$ 1.7)	2.7 m & 3.15 m	8.15-8.2 (e)	8.45 dd ($J_{8,9}$ 8.2, $J_{8,10}$ 1.5)	8.15 dd ($J_{8,9}$ 8.4)	8.7 dd ($J_{8,9}$ 8.3, $J_{8,10}$ 1.2)
11	8.15 d ($J_{10,11}$ 9.5) (J10,11, 9.5)				~7.3 m (e)	8.3 dd ($J_{10,11}$ 8.4)	7.9 dd ($J_{10,11}$ 8.3, $J_{9,11}$ 1.2)
9		7.45 dd ($J_{8,9}$ 8.8, $J_{9,10}$ 7.3)	1.8-2.0 m	7.7 (g) ($J_{9,11}$ 1.7)	~7.25 m (e)	7.7 m	7.3 ddd ($J_{8,9}$ 8.5, $J_{9,10}$ 6.9, $J_{9,11}$ 1.3)
10	7.5 (e)	7.20 dd ($J_{9,10}$ 7.3, $J_{8,10}$ 1.7)		7.4 (g) ($J_{8,10}$ 1.7)	7.65 ddd ($J_{10,11}$ 8.3, J9,10 6.7, $J_{8,10}$ 1.5)	7.55 m	7.65 ddd ($J_{10,11}$ 8.5, $J_{9,10}$ 6.9, $J_{8,10}$ 1.3)
CH_3	2.95	2.9	2.4	2.9			

(a) Chemical Shifts in ppm downfield from tetramethylsilane and, in parentheses coupling constants in Hz; measured in deuteriochloroform solvent except for **2** DMSO-d_6 and **12** (1:2 DMSO-d_6-deuteriochloroform). (b) Assignments established by decouplings. For **2** irradiation at 8.17 sharpened the signal at δ 7.5. Irradiation at 8.11 collapsed a doublet at δ 7.8 and irradiation at δ 7.5 gave a sharp singlet at δ 8.17. Irradiation of **3** at δ 9.3 collapsed the doublet (J 1.5 Hz) due to W-coupling at δ 7.55 while irradiation at δ 7.18 removed the smaller splitting in the doublet of doublet signals at δ 7.45 and δ 7.6. (c) Tentative assignments of protons 8-11 based on comparison with **1** (5). (d) Width-at-half-height = 11-12 Hz. (e) Partly masked by other signals. (f) $J_{1,5}$ (W-coupling) collapsed on irradiation of H-1. (g) Approx ddd; tentative assignment of H-9 *vs.* H-10 being based on analogy with **1** (5).

other products in the hydrogenation were more reduced materials (^{1}H nmr analysis), it was obvious that preparation of the A-ring tetrahydro-compound **7** required an alternative approach.

Our synthesis of 1,2,3,4-tetrahydro-7-methylbenz[*c*]acridine (**7**) is based on Campbell and Morgan's synthesis of 7-methylbenz[*c*]acridine (7). The Ullman reaction (8) of 5,6,7,8-tetrahydro-1-napthylamine (8) with potassium *o*-bromobenzoate gave the diarylamine *o*-carboxylate **9** which was readily cyclised by polyphosphoric acid or by phosphorus oxychloride to give respectively, the acridone **10** or the chloroacridine derivative **11**. These two products are interconvertable using hydrochloric acid in ethanol (**11** → **10**) and phosphorus oxychloride (**10** → **11**). Displacement of chlorine from the chloroacridine **11** by sodiomalononitrile (7) yielded the aryl-substituted malononitrile (existing in the "acridone-form" **12**) (9). From this product 1,2,3,4-tetrahydro-7-methylbenz-[*c*]acridine (**7**) was obtained by hydrolysis in sulfuric acid (10).

EXPERIMENTAL

The ^{1}H data were collected using a JEOL FX-90Q spectrometer operating at 89.6 MHz in the Fourier-transform mode or a Varian HA100 spectrometer. For the former, about 60° pulse angles, pulse interval is 5.5 s, and 8K data points were employed. Methane chemical-ionisation mass spectra were obtained using a Finnigan 3200 E gas-chromatograph mass-spectrometer with the associated Finnigan 6110 data system; electron-impact mass spectra were obtained using an A. E. I. MS-902 mass spectrometer operating at 70 eV.

In the working-up procedures, washing and drying of organic solutions refer to water and anhydrous sodium sulfate respectively. Evaporation of organic solvents took place under reduced pressure. Melting points were uncorrected.

Each product described below showed the correct MH^+ ion in the methane chemical-ionisation ms, and gave a ^{1}H nmr spectrum which was compatible with the structure. Below ms data refers to electron-impact ms. ^{1}H Nmr data are to be found in Table 1.

9-Hydroxy-7-methylbenz[*c*]acridine (**2**).

N-(*p*-Methoxyphenyl)-1-napthylamine (**4**) (6) (3.9 mmoles, 1.0 g) 1.0 g of acetic anhydride (10 mmoles) and 2.7 g of anhydrous zinc chloride (20 mmoles) were heated in a sealed tube at 225° for 5 hours. The tar-like reaction mixture was distributed between 2*M* sodium hydroxide and chloroform. The aqueous phase was extracted with chloroform, adjusted to *p*H 8 and then re-extracted with chloroform. The last chloroform extract was washed repeatedly with 0.5*M* sulfuric acid, the acid washings were adjusted to *p*H 7 and the precipitate which formed (0.30 g, 28%) was crystallised from chloroform to give 9-hydroxy-7-methylbenz[*c*]-acridine (**2**) as needles of the chloroform hemisolvate, mp 240-257° dec (with change to cubes at 190°); ir (Nujol): 3080-3300 cm^{-1} (OH), ms: 259.1000 (M^+, 100), 258 (12), 230 (6), 228 (5), 129.5 (M^+/2e,7); calcd. M^+ for

$C_{18}H_{13}NO$: 259.0998; ^1H nmr DMSO-d_6 δ 8.3 due to $\frac{1}{2}CHCl_3$ (see also Table 1).

Anal. Calcd. for $C_{18}H_{13}NO \cdot \frac{1}{2}CHCl_3$: C, 69.63; H, 4.27; N, 4.39; Cl, 16.7. Found: C, 69.67; H, 4.63; N, 4.40; Cl, 14.5.

The phenol **2** was converted to 9-acetoxy-7-methylbenz[*c*]acridine by treatment with excess acetic anhydride in dry pyridine overnight. The acetate crystallized from methylene chloride-petroleum spirit to give long needles, mp 168-170°.

Anal. Calcd. for $C_{20}H_{15}NO_2$: C, 79.72; H, 5.02; N, 4.65. Found: C, 80.00; H, 5.26; N, 4.70.

11-Hydroxy-7-methylbenz[*c*]acridine (**3**).

N-(*o*-Methoxyphenyl)-1-naphthylamine (**5**) (6) (3.9 mmoles) was reacted with acetic anhydride and zinc chloride as described above for the preparation of **2**. The tarry reaction mixture was treated with chloroform and 5*M* sodium hydroxide. The chloroform phase was washed with water, concentrated and applied to preparative tlc plates. The phenolic fraction (blue colour with ½% ferric ferricyanide) was dissolved in chloroform, extracted into 3*M* sulfuric acid, and re-isolated from the aqueous phase by chloroform extraction after adjustment of the *p*H to 6. On crystallisation from chloroform-light petroleum, 36 mg (4%) of 11-hydroxy-7-methylbenz[*c*]acridine (**3**), mp 169-172° was obtained; ir (Nujol): 3330 cm^{-1} (OH); ms: 259.0994 (M^+, 100), 231 (14), 230 (16), 228 (4); calcd. M^+ for $C_{18}H_{13}NO$: 259.0998.

Anal. Calcd for $C_{18}H_{13}NO$: C, 83.37; H, 5.05; N, 5.40. Found: C, 83.08; H, 5.53; N, 5.72.

The phenol **3** was converted to 11-acetoxy-7-methylbenz[*c*]acridine as described above affording needles, mp 179-182°.

Anal. Calcd. for $C_{20}H_{15}NO_2$: C, 79.72; H, 5.02; N, 4.65. Found: C, 79.68; H, 5.14; N, 4.44.

8,9,10,11-Tetrahydro-7-methylbenz[*c*]acridine (**6**).

Adams catalyst and 7.5 g of 7-methylbenz[*c*]acridine dissolved in 55 ml of trifluoroacetic acid were shaken at room temperature and under hydrogen at 3 atmospheres for 2 hours. After removal of the catalyst by filtration the solution was neutralised with 2*M* sodium hydroxide and then extracted with chloroform. The residue obtained on evaporation of the washed and dried chloroform solution was purified by crystallisation from diethyl ether followed by chromatograhy over silica gel to give 2.0 g (27%) of 8,9,10,11-tetrahydro-7-methylbenz[*c*]acridine (**6**), mp 120-121°, ms: 247 (M^+, 100) 232 (20).

Anal. Calcd. for $C_{18}H_{17}N$: C, 87.45; H, 6.88; N, 5.67. Found: C, 87.22; H, 6.95; N, 5.62.

N-(5,6,7,8-Tetrahydro-1-napthyl)-*o*-aminobenzoic acid (**9**).

Potassium *o*-bromobenzoate [obtained by evaporation of a solution of 30.0 g of *o*-bromobenzoic acid (0.15 mole) and of 10.3 g of potassium carbonate in 250 ml of ethanol] was refluxed in 120 ml of amyl alcohol with 23.0 g of 5,6,7,8-tetrahydro-1-naphthylamine (**8**) (0.156 mole) in the presence of 0.75 g of copper (from aqueous cupric sulfate and zinc dust) (7) for 10 hours. After evaporation of the amyl alcohol under reduced pressure at 90°, water was added and the basic solution was extracted with light petroleum to remove the unreacted tetrahydronaphthylamine. After adjustment to *p*H 6 with hydrochloric acid, the aqueous solution was extracted with ethyl acetate. The residue on evaporation of the washed and dried ethyl acetate solution was crystallised from benzene to give 20 g of *N*-(5,6,7,8-tetrahydro-1-napthyl)-*o*-aminobenzoic acid (**9**) as needles, mp 184-185°; ir (Nujol): 3315 cm^{-1} (NH), 1650 cm^{-1} (C=O); ms: 267 (M^+, 100), 248 (85), 234 (40), 221 (20), 220 (25). On chromatography of the mother liquors over silica gel, a further 6 g was obtained to give a total yield of 65%.

Anal. Calcd. for $C_{17}H_{17}NO_2$: C, 76.40; H, 6.37; N, 5.24. Found: C, 76.48; H, 6.57; N, 5.20.

1,2,3,4-Tetrahydrobenz[*c*]acridone (**10**).

(a) A mixture of 0.5 g of the acid **9** and 3 g of polyphosphoric acid was maintained at 80° with stirring and protection from moisture for 3 hours. When cooled, the mixture was poured into ice-cold water and extracted with ethyl acetate. Evaporation of the washed and dried ethyl acetate gave 0.3 g (65%) of 1,2,3,4-tetrahydrobenz[*c*]acridone (**10**) which crystallised from ethanol-light petroleum as needles, mp 298-302°; ir (Nujol); 3280 cm^{-1} (NH); ms: 249 (M^+, 100), 221 (20).

Anal. Calcd. for $C_{17}H_{15}NO$: C, 81.93; H, 6.02; N, 5.62. Found: C, 81.55; H, 5.67; N, 5.98.

(b) The chloro-compound **11** (see below) was refluxed in 90% ethanol (5.0 ml) containing 10*M* hydrochloric acid (1 drop) for half an hour. On cooling, the acridone **10** was obtained in 66% yield, showing ^1H nmr spectrum identical with that of a sample prepared from the acid **9** (see above).

1,2,3,4-Tetrahydro-7-chlorobenz[*c*]acridine (**11**).

(a) A solution of 10 g of the acid **9** in 50 ml of phosphorus oxychloride was refluxed for 2 hours. After removal of solvent, an ice-cold mixture of aqueous ammonia and chloroform was added. The chloroform layer was washed, dried and evaporated to give a residue which was purified by chromatography over alumina and crystallisation from benzene to give 5 g (50%) of yellow needles of 1,2,3,4-tetrahydro-7-chlorobenz[*c*]acridine, mp 107-108°, ms: 269, 267 (M^+ 35, 98), 268, 266 (50, 100). 252 (60).

Anal. Calcd. for $C_{17}H_{14}ClN$: C, 76.26; H, 5.23; N, 5.23. Found: C, 75.83; H, 5.20; N, 5.27.

(b) The acridone **10** was treated as in (a) above to give the chloro-compound **11** having ^1H nmr identical with that of a sample prepared from the acid **9**.

1,2,3,4-Tetrahydro-7-methylbenz[*c*]acridine (**7**).

To a solution of 0.5 g of sodium in anhydrous butanol was added a solution of 1.8 g of the chloro-compound **11** (6.7 mmoles) in 10 ml of xylene followed by 1.3 g of malononitrile (19.7 mmoles). After the mixture was refluxed for 16 hours, the solvent was evaporated and the resulting residue washed with aqueous acetic acid and then with a small amount of ethyl acetate leaving crude 1,2,3,4-tetrahydro-7-dicyanomethylbenz[*c*]acridine (**12**), mp 269-270° (90% yield); ir (Nujol): 3300 cm^{-1} (NH), 2205 and 2195 cm^{-1} (C≡N). This was satisfactory for the transformation below. The product gave in the methane chemical-ionization ms an ion at 298 (MH^+).

A mixture of 1.5 g of the crude dicyano-compound **12** in 10*M* sulfuric acid was gently refluxed with stirring for 2 hours.

The cooled mixture was poured with stirring into an ice-cold mixture of aqueous ammonia and chloroform. The aqueous layer was extracted several times with chloroform and the combined chloroform solutions washed, dried and evaporated.

Crystallisation of the residue from ethanol gave 0.7 g of 1,2,3,4-tetrahydro-7-methylbenz[*c*]acridine (**7**). A further 0.4 g was obtained by chromatography of the mother liquors over silica gel, giving a total of 88% yield. The product has mp 113-114°, ms: 247 (M^+, 100), 246 (98), 232 (45), 231 (15), 230 (15), 218 (15).

Anal. Calcd. for $C_{18}H_{17}N$: C, 87.45; H, 6.88; N, 5.67. Found: C, 87.24; H, 6.94; N, 5.62.

Acknowledgment.

The financial support of the Australian Tobacco Research Foundation is gratefully acknowledged. We also thank Drs. I. R. Brown and A. V. Robertson of the School of Chemistry, University of Sydney for the electron-impact mass spectra, and Dr. Tu Hoa Ai for some of the nmr data.

REFERENCES AND NOTES

(1a) A. Lacassagne, N. P. Buu-Hoi, R. Daudel and F. Zajdela, *Adv. Cancer Res.*, **4**, 315 (1956); (b) H. R. Glatt, H. Schwind, F. Zajdela, A. Croisy, P. C. Jacquignon and F. Oesch, *Mutat. Res.*, **66**, 307 (1979).

(2) C. M. Ireland, H. T. A. Cheung, G. M. Holder and A. J. Ryan, *Chem.-Biol. Interac.*, **40**, 305 (1982).

(3) I. A. Smith and P. G. Seybold, *J. Heterocyclic Chem.*, **16**, 421, (1979), and references cited therein.

(4) L. J. Boux, H. T. A. Cheung, G. M. Holder and L. Moldovan, *Tetrahedron Letters*, **21**, 2921 (1980).

(5) H. T. A. Cheung, G. M. Holder and L. Moldovan, *J. Labelled Comp. Radiopharm.*, **17**, 121 (1980), and literature cited therein.

(6) E. Knoevenagel, *J. Prakt. Chem.*, **89**, 1 (1914).

(7) A. Campbell and E. N. Morgan, *J. Chem. Soc.*, 1711 (1958).

(8) J. M. F. Gagan in "The Chemistry of Heterocyclic Compounds", A. Weissberger and E. C. Taylor eds, 2nd ed. Vol 9, Wiley-Interscience, New York, 1973, p 160-165.

(9) The dicyano-compound is written here in the "acridone-form" on the basis of ^{1}H nmr [absence of a signal for $^-C\mathit{H}(CN)_2$ and general similarity to the spectrum of the acridone **10**] and ir spectra [presence of NH absorption].

(10) When this work was completed, the conversion of benz[*c*]acridine to 1,2,3,4-tetrahydrobenz[*c*]acridine by sodium-alcohol reduction followed by re-oxidation of the heterocyclic ring was reported: R. E. Lehr and S. Kumar, *J. Org. Chem.*, **46**, 3675 (1981).

(11) R. M. Acheson in "The Chemistry of Heterocyclic Compounds", A. Weissberger and E. C. Taylor, eds, 2nd ed, Vol. 9, Wiley-Interscience, New York, 1973, p 692-696.