Synthesis and Spontaneous Racemization of Benz[*a*]anthracene 1,2-Oxide

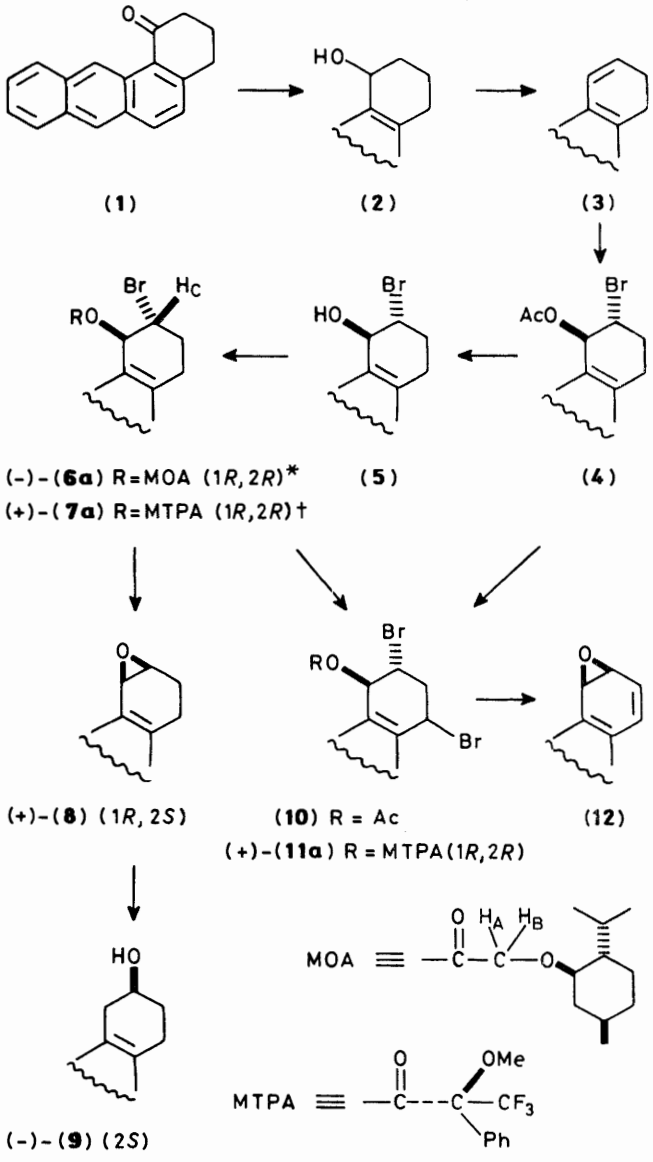
Derek R. Boyd * and Narain D. Sharma
Department of Chemistry, The Queen's University of Belfast, Belfast BT9 5AG, N. Ireland

Benz[*a*]anthracene 1,2-oxide (1,2-epoxy-1,2-dihydrobenz[*a*]anthracene), a minor metabolite of benz[*a*]anthracene in hepatic systems, has been synthesized both from racemic precursors and from separated diastereoisomeric bromohydrin esters whose absolute stereochemistry has been determined by n.m.r. methods. The benz[*a*]anthracene 1,2-oxide obtained was racemic as previously predicted from PMO calculations.

The carcinogenic polycyclic aromatic hydrocarbon benz[*a*]-anthracene (B[*a*]A) was found to be extensively epoxidized in the presence of mono-oxygenase enzymes from animal liver systems. Thus, the range of *trans*-dihydrodiol metabolites detected and isolated indicated that epoxides were initially formed at the 1,2-, 3,4-, 5,6-, 8,9-, and 10,11-bonds of B[*a*]A.[1] Preliminary PMO calculations[2,3] led to the prediction that the 5,6-, 8,9-, and 10,11-oxides of B[*a*]A would be configurationally stable and thus isolable as enantiomers. This has recently been confirmed by the synthesis of pure enantiomers in each case.[4–6] The availability of both enantiomers of B[*a*]A 8,9- and 5,6-oxide has also been used to confirm that addition of an oxygen atom to B[*a*]A occurs by almost exclusive attack from one prochiral face under the catalytic influence of a hepatic mono-oxygenase enzyme.[7]

Relatively little attention has been paid to the metabolites of B[*a*]A at the 1,2-position since the *trans*-1,2-dihydrodiol (and thus the 1,2-oxide precursor) is the least abundant metabolite and has shown little tumourogenic or mutagenic activity compared with the other metabolically formed dihydrodiols of B[*a*]A. Several studies on the metabolism of the *trans*-1,2-dihydrodiol metabolite of B[*a*]A by rat-liver microsomes have recently been carried out.[8,9] A major objective of the present study was to synthesize B[*a*]A 1,2-oxide (1,2-epoxy-1,2-dihydro-B[*a*]A), both from racemic and optically pure precursors, and to demonstrate that spontaneous racemization of the optically active arene oxide had occurred as predicted by the PMO method.[2,3]

The synthesis of B[*a*]A 1,2-oxide (**12**) from 3,4-dihydrobenz[*a*]anthracen-1(2*H*)-one (**1**) was carried out by the reaction sequence shown in the Scheme. This synthetic route is similar in concept to that previously reported for the synthesis of optically pure arene oxides in the naphthalene (1,2-[8]), anthracene (1,2-[8]), benz[*a*]anthracene (8,9-,[4] 10,11-[5]), and benzo[*a*]pyrene (8,9-[9]) series. In the present example however the synthesis was more difficult owing to the generally greater instability of the compounds. Thus, the olefin (**3**) and the bromohydrin (**5**) could not be prepared in good yield by the normal[4,5,8,9] synthetic methods, and these had to be modified. The dibromoesters (**10**) and (**11a**) could not be purified by chromatography or recrystallization without decomposition, and were used immediately after isolation. The arene oxide (**12**), in contrast to the previously synthesized 5,6-,[5] 8,9-,[6] and 10,11-[5] arene oxides of B[*a*]A, proved to be extremely unstable in the crystalline state. Instability again precluded the synthesis and purification of *trans*-1,2-dihydroxy-1,2,3,4-tetrahydro-B[*a*]A by hydrolysis of the tetrahydroepoxide (**8**) under the conditions previously used.[4,5,10,11] Despite these problems of instability, however, the racemic arene oxide (**12**) was obtained from the olefin (**3**) in three steps, (**3**) ⟶ (**4**) ⟶ (**10**) ⟶ (**12**), with an overall yield of *ca.* 33%.



Scheme. * (+)-(**6b**) R = MOA (1*S*,2*s*). † (−)-(**7b**) R = MTPA (1*S*,2*S*)

Optically active precursors of B[*a*]A 1,2-oxide were obtained by separation of the individual diastereoisomers of the menthyloxyacetate (MOA) [(**6a**) and (**6b**)] and 2-methoxy-2-phenyl-2-trifluoromethylacetate (MTPA) [(**7a**) and (**7b**)] esters of the bromohydrin (**5**) using preparative h.p.l.c. or fractional

crystallization methods. As found for the corresponding bromohydrin esters in other members of the polycyclic aromatic hydrocarbon series,[11] the bromo-MOA diastereoisomers were more difficult to separate [*e.g.* (**6a**) and (**6b**), α = 1.40] than the corresponding MTPA diastereoisomers [*e.g.* (**7a**) and (**7b**), α = 1.83] by h.p.l.c. The relatively small samples of the pure crystalline diastereoisomers (**6a**) and (**6b**) [or (**7a**) and (**7b**)] obtained initially by preparative h.p.l.c. provided seed crystals which enabled larger quantities of each diastereoisomer to be separated by fractional recrystallization.

The absolute stereochemistry of the individual diastereoisomers in each of the pairs (**6a**)/(**6b**) and (**7a**)/(**7b**) was determined by n.m.r. methods which have been used successfully for similar bromo-MOA and bromo-MTPA derivatives[4,5,10–12] (250 MHz; C_6D_6). Thus the bromo-MOA ester eluted early by h.p.l.c. {(**6a**), $[\alpha]_D$ −143°} showed a characteristic singlet (δ 3.88) due to the exocyclic methylene protons (H_AH_B) and was assigned a (1*R*,2*R*) configuration; the late diastereoisomer {(**6b**), $[\alpha]_D$ +82°} was similarly assigned a (1*S*,2*S*) configuration due to the presence of an AB quartet (centred at δ 3.79 and 3.88, J_{AB} 16.5 Hz). In studies of a range of bromo-MTPA esters[10] analogous to (**7a**) and (**7b**), the early isomer, (**7a**), showed a smaller positive δ value for the proton H_C in the ^{1}H n.m.r. spectrum (δ 4.68) and a smaller negative δ value of CF_3 in the ^{19}F n.m.r. spectrum (δ −8.39) which was consistent with a (1*R*,2*R*) configuration. Conversely, the (1*S*,2*S*) configuration was associated with the later isomer (**7b**) which gave a larger positive δ value for H_C (4.83) and a larger negative δ value for CF_3 (δ −8.73). These configurational assignments were verified by treatment of (+)-(1*R*,2*R*)-(**7a**) with NaOMe to yield the tetrahydroepoxide (+)-(**8**); the (−)-enantiomer of compound (**8**) was obtained by similar treatment of (+)-(1*S*,2*S*)-(**6b**). This stereochemical correlation indicates that (+)-(**8**) must have a (1*R*,2*S*) configuration and that the alcohol (**9**) obtained by $LiAlH_4$ reduction must have (−)-(2*S*) stereochemistry.

The benzylic bromination reaction of (+)-(**7a**) using *N*-bromosuccinimide in CCl_4, and the cyclization reaction with NaOMe, were carried out directly without purification of the unstable intermediate (**11a**). The arene oxide (**12**) thus derived from (+)-(**7a**), was obtained as white crystals from tetrahydrofuran (THF)–pentane in 52% yield, and showed a very small optical rotation ($[\alpha]_D \leqslant +4°$). This optical rotation did not decrease with time (*i.e.* gave no evidence of spontaneous racemization), and could be accounted for by a trace of (+)-(**8**) ($[\alpha]_D$ +197°) which was detected in the n.m.r. spectrum. This trace impurity resulted from incomplete bromination of (+)-(**7a**) and could not be removed. Since the $[\alpha]_D$ values for the configurationally stable enantiomers of arene oxides of naphthalene, anthracene, benz[*a*]anthracene, and benzo[*a*]pyrene previously reported were in the range $[\alpha]_D$ ±150 ⟶ ±400°, it may reasonably be concluded that the sample of the oxide (**12**) prepared from (**11a**) is totally racemic. This result is in accord with the PMO predictions based upon the assumption that spontaneous racemization of (**12**) occurs. While mammalian metabolism of B[*a*]A appears to occur to a minor degree at the 1,2-bond,[1] bacterial metabolism shows a strong preference for this position.[13] The resolution and stereochemical assignments in the present study have been used in the determination of the absolute stereochemistry of the major bacterial metabolite of B[*a*]A, *cis*-1,2-dihydroxy-1,2-dihydrobenz[*a*]anthracene, and will be discussed elsewhere.[14]

Experimental

^{1}H N.m.r. spectra were obtained at 250 MHz using a Bruker WM 250 instrument in $CDCl_3$ solution with tetramethylsilane as reference unless stated otherwise. The ^{19}F n.m.r. spectra were obtained in $CDCl_3$ solution using a Varian XL-100 instrument (94.2 MHz) with α,α,α,-trifluorotoluene as reference. Optical rotation measurements were recorded in $CHCl_3$ or $CDCl_3$ solution at 254 nm using a model 241 Perkin-Elmer automatic polarimeter.

Separation of the diastereoisomers (**6a**)/(**6b**) or (**7a**)/(**7b**) was achieved using Spectra Physics (model 3500B) and Perkin-Elmer (model 3B) instruments. Analytical and preparative separations were carried out using DuPont Zorbax-Sil columns (6.2 mm × 250 mm and 9.4 mm × 500 mm, respectively).

3,4-Dihydrobenz[*a*]anthracen-1(2*H*)-one, (−)-menthyloxyacetic acid, and (−)-2-methoxy-2-phenyl-2-trifluoromethylacetic acid were obtained from Aldrich. The corresponding (−)-acetyl chlorides were obtained by standard methods.

(±)-1-*Hydroxy*-1,2,3,4-*tetrahydrobenz*[a]*anthracene* (**2**).—A suspension of 3,4-dihydrobenz[*a*]anthracen-1(2*H*)-one (18 g) in methanol (400 ml) was stirred at room temperature with sodium borohydride (4 g) for 4 h. The solution was concentrated under reduced pressure and the *alcohol* (**2**) was filtered and recrystallized from methanol to yield light yellow crystals (17 g, 93%), m.p. 133—134 °C (Found: C, 86.9; H, 6.6. $C_{18}H_{16}O$ requires C, 87.1; H, 6.5%); δ 1.68—2.39 (4 H, m, 2- and 3-H), 2.74—2.98 (2 H, m, 4-H), 5.52 (1 H, m, 1-H), 7.06—8.02 (6 H, m, aryl H), 8.30 (1 H, s, 7-H), and 8.72 (1 H, s, 12-H).

3,4-*Dihydrobenz*[a]*anthracene* (**3**).—The dehydration of compound (**2**) was effected by the addition of toluene-*p*-sulphonic acid (0.01 g) to a refluxing solution of (**2**) (1.75 g) in benzene (50 ml). Azeotropic removal of water using a Dean–Stark apparatus was complete after 0.5 h. The *olefin* (**3**) was obtained (1.2 g, 74%) as a light yellow powder by concentration and recrystallization from chloroform–hexane, m.p. 97—98 °C (Found: C, 93.7; H, 6.1. $C_{18}H_{14}$ requires C, 93.9; H, 6.1%); δ 2.26—2.59 (2 H, m, 3-H), 2.83—3.11 (2 H, m, 4-H), 6.25—6.42 (1 H, m, 2-H), 7.32—8.06 (7 H, m, 2-H and aryl H), 8.36 (1 H, s, 7-H), and 8.63 (1 H, s, 12-H).

(±)-trans-1-*Acetoxy*-2-*bromo*-1,2,3,4-*tetrahydrobenz*[a]*anthracene* (**4**).—To a stirred solution of compound (**3**) (1.4 g) in glacial acetic acid (35 ml) at room temperature, was added lithium acetate (1.1 g) and *N*-bromoacetamide (0.925 g). After the mixture had been stirred for 0.75 h the bromoacetate (**4**) was precipitated by the addition of crushed ice (100 g). The filtered and dried *product* (**4**) was recrystallized from chloroform–hexane as light yellow needles (1.4 g, 62%), m.p. 142—144 °C (Found: C, 64.8; H, 4.6. $C_{20}H_{17}BrO_2$ requires C, 65.0; H, 4.6%); δ 2.07 (3 H, s, OAc), 2.20—2.74 (2 H, m, 3-H), 2.94—3.61 (2 H, m, 4-H), 4.74 (1 H, m, 2-H), 6.88 (1 H, d, $J_{1,2}$ 2.2 Hz, 1-H), 7.18—8.02 (6 H, m, aryl H), 8.31 (1 H, s, 7-H), and 8.31 (1 H, s, 12-H).

(±)-trans-1-*Acetoxy*-2,4-*dibromo*-1,2,3,4-*tetrahydrobenz*[a]*anthracene* (**10**) *and Derived* (±)-*Benz*[a]*anthracene* 1,2-*Oxide* (**12**).—The bromoacetate (**4**) (0.2 g) was converted into the dibromoacetate (**10**) by treatment with *N*-bromosuccinimide (0.105 g) in refluxing CCl_4. Attempts to purify the product (**10**) resulted in decomposition. The crude dibromoacetate (**10**) (0.2 g) yielded the arene oxide (**12**) on stirring with NaOMe (0.2 g) in THF solution (10 ml) at 0 °C for 4 h. Recrystallization from THF–pentane gave (±)-(**12**) as colourless needles (0.068 g, 75%), m.p. 126—130 °C (decomp.); δ 4.28 (1 H, m, $J_{1,2} = J_{2,3}$ 3.9, $J_{2,4}$ 1.7 Hz, 2-H), 5.32 (1 H, d, $J_{1,2}$ 3.9 Hz, 1-H), 6.54 (1 H, dd, $J_{3,2}$ 3.9 Hz, $J_{3,4}$ 9.5 Hz, 3-H), 6.86 (1 H, dd, $J_{4,3}$ 9.5 Hz, $J_{4,2}$ 1.9 Hz), 7.37—8.20 (6 H, m, aryl H), 8.13 (1 H, s, 7-H), and 8.97 (1 H, s, 12-H).

(±)-trans-2-*Bromo*-1-*hydroxy*-1,2,3,4-*tetrahydrobenz*[a]-*anthracene* (**5**).—The conversion of the bromoacetate (**4**) (1.0 g) into the bromohydrin (**5**) was carried out using an excess of diborane in THF by the normal method.[10] Recrystallization from chloroform–hexane gave the *bromohydrin* (**5**) (0.665 g, 75%), m.p. 137—139 °C (Found: C, 66.0; H, 4.6. $C_{18}H_{15}BrO$ requires C, 66.1; H, 4.6%); δ 2.22—2.89 (2 H, m, 3-H), 2.93—3.78 (2 H, m, 4-H), 4.77 (1 H, m, 2-H), 5.72 (1 H, m, 1-H), 7.09—8.16 (6 H, m, aryl H), 8.39 (1 H, m, 7-H), and 8.72 (1 H, s, 12-H).

(−)-(1R,2R)- *and* (+)-(1S,2S)-trans-2-*Bromo*-1-*menthyloxyacetoxy*-1,2,3,4-*tetrahydrobenz*[a]*anthracene* (**6a**) *and* (**6b**).—Treatment of the (±)-bromohydrin (**5**) (0.2 g) with (−)-menthyloxyacetyl chloride in pyridine solution yielded a diastereoisomeric mixture of (**6a**) and (**6b**) which was purified by column chromatography on silica gel (0.27 g, 85%), m.p. 105—108 °C, recrystallized from diethyl ether–pentane (Found: C, 69.0; H, 6.9. $C_{30}H_{35}BrO_3$ requires C, 68.8; H, 6.7%). Isomers (**6a**) and (**6b**) were separated by preparative h.p.l.c. using cyclohexane–diethyl ether (96:4) as eluant (α 1.40). Using seed crystals of (**6a**) and (**6b**) it was possible to separate these diastereoisomers by fractional recrystallization from diethyl ether–pentane. Early *isomer* (**6a**), m.p. 105—107 °C (recrystallized from diethyl ether–pentane, 1:10, at −40 °C), $[\alpha]_D$ −143°, (1*R*,2*R*); δ 0.60—2.31 (19 H, m, menthyl group), 2.45 (2 H, m, 3-H), 2.87 (1 H, m, 4-H), 3.16 (1 H, m, 4-H), 3.88 (2 H, s, H_A and H_B), 4.55 (1 H, m, 2-H), 7.16—7.78 (7 H, m, 1-H and aryl protons), 8.08 (1 H, s, 7-H), and 8.57 (1 H, s, 12-H). Late *isomer* (**6b**), m.p. 134—136 °C (recrystallized from diethyl ether–pentane, 1:4), $[\alpha]_D$ +82°, (1*S*,2*S*); δ values similar to (**6a**) except for signals at δ 3.79 (1 H, d, J_{AB} 16.5 Hz, H_A) and 3.88 (1 H, d, J_{BA} 16.5 Hz, H_B).

(+)-(1R,2R)- *and* (−)-(1S,2S)-trans-2-*Bromo*-1-[2-*methoxy*-2-*phenyl*-2-*trifluoromethylacetoxy*]-1,2,3,4-*tetrahydrobenz*[a]-*anthracene* (**7a**) *and* (**7b**).—The reaction of the (±)-bromohydrin (**5**) (3 g) with (−)-2-methoxy-2-phenyl-2-trifluoromethylacetyl chloride (3 g) in pyridine (8 ml) yielded a mixture of diastereoisomers (**7a**) and (**7b**) which was purified by column chromatography on silica gel (4.5 g, 90%), m.p. 125—132 °C (Found: C, 61.6; H, 4.1. $C_{28}H_{22}BrF_3O_3$ requires C, 61.9; H, 4.1%). Isomers (**7a**) and (**7b**) were separated by h.p.l.c. using cyclohexane–diethyl ether (97:3) as eluant (α 1.83). Fractional recrystallization of the mixture, (**7a**) and (**7b**), from chloroform–hexane was also found to yield pure samples of each diastereoisomer: *isomer* (**7a**), m.p. 147—149 °C, $[\alpha]_D$ +36°, (1*R*,2*R*); δ 2.05—2.15 (2 H, m, 3-H), 2.72—3.29 (2 H, m, 4-H), 3.38 (3 H, br s, OMe), 4.68 (1 H, m, 2-H), 7.09—8.01 (7 H, m, 1-H and aryl H), and 8.39 (2 H, m, 7-H and 12-H); δ_F −8.39. *Isomer* (**7b**), m.p. 159—161 °C, $[\alpha]_D$ −21°, (1*S*,2*S*); δ 2.20—2.56 (2 H, m, 4-H), 3.38 (3 H, br s, OMe), 4.83 (1 H, m, 2-H), 7.16—7.89 (7 H, m, 1-H and aryl H), 8.36 (1 H, s, 7-H), and 8.37 (1 H, s, 12-H); δ_F −8.73.

(±)-*Benz*[a]*anthracene* 1,2-*Oxide* (**12**) *from* (+)-(**7a**) *and* (+)-(**11a**).—Bromination of compound (**7a**) (0.13 g, $[\alpha]_D$ +36°) under similar conditions to those used in the synthesis of (**10**) gave the dibromo-MTPA ester (**11a**) (0.1 g, 66%, $[\alpha]_D$ +53°) in crude form. As with compound (**11a**), attempts to purify the sample either by chromatography or recrystallization resulted in decomposition. The crude form of (**11a**) was thus used to form the arene oxide (**12**) (0.03 g, 77%). Recrystallization from THF–pentane at low temperature gave colourless needles of (**12**), m.p. 126—130 °C (decomp.), $[\alpha]_D$ +3.8°. The sample gave an identical n.m.r. spectrum to the racemic sample of (**12**) obtained from (**10**), but traces of the reduced analogue (**8**) were detected which may account for the small but constant residual $[\alpha]_D$ value.

(+)-(1R,2S)-1,2-*Epoxy*-1,2,3,4-*tetrahydrobenz*[a]*anthracene* (**8**).—The synthesis of the epoxide (**8**) from the corresponding bromo-ester (**7a**) (0.25 g, $[\alpha]_D$ +36°) was carried out in the normal manner using NaOMe in Et_2O. The *product* (**8**) was recrystallized from diethyl ether to yield white needles (0.075 g, 66%), m.p. 135—137 °C, $[\alpha]_D$ +197° (Found: C, 87.6; H, 5.9. $C_{18}H_{14}O$ requires C, 87.8; H, 5.7%). The (±)-epoxide (**8**) prepared from (±)-(**4**) by the same method showed m.p. 109—110 °C. Using the MOA ester (**6b**) (0.03 g, $[\alpha]_D$ +82°) as the precursor, a crude sample of (−)-(**8**) ($[\alpha]_D$ −183°), was obtained as a light yellow powder (0.01 g, 71%). The samples of (+)- and (±)-(**8**) all gave identical n.m.r. spectra; δ 1.86—2.10 (2 H, m, 3-H), 2.43—3.02 (2 H, m, 4-H), 3.92 (1 H, m, 2-H), 4.86 (1 H, d, J_{12}, 4.4 Hz 1-H), 7.16—8.09 (6 H, m, aryl H), 8.41 (1 H, s, 7-H), and 8.83 (1 H, s, 12-H).

(−)-(2S)-2-*Hydroxy*-1,2,3,4-*tetrahydrobenz*[a]*anthracene* (**9**).—The reduction of (+)-(**8**) (0.04 g, $[\alpha]_D$ +197°) using $LiAlH_4$ in diethyl ether solvent yielded the *product* (−)-(**9**) as colourless crystals from diethyl ether (0.025 g, 62%), m.p. 158—159 °C, $[\alpha]_D$ −33°, (2*S*) (Found: C, 86.8; H, 6.6. $C_{18}H_{16}O$ requires C, 87.1; H, 6.5%); δ 1.54—2.32 (2 H, m, 3-H), 2.89—3.83 (4 H, m, 1-H and 4-H), 4.37 (1 H, m, 2-H), 7.14—8.06 (6 H, m, aryl H), 8.36 (1 H, s, 7-H), and 8.45 (1 H, s, 12-H).

Acknowledgements

We wish to thank Dr. L. Waring for the 250 MHz ^1H n.m.r. spectra, Dr. W. B. Jennings for the ^{19}F spectra, and Mr. B. McKnight for the microanalytical data. We also gratefully acknowledge postdoctoral support from the S.E.R.C. (to N. D. S.) and funds from the Nuffield Foundation and the S.E.R.C. to purchase h.p.l.c. columns and equipment, respectively.

References

1 D. R. Thakker, W. Levin, H. Yagi, S. Turujman, D. Kapidia, A. H. Conney, and D. M. Jerina, *Chem.-Biol. Interact.*, 1979, **27**, 145.
2 D. R. Boyd, J. D. Neill, and M. E. Stubbs, *J. Chem. Soc., Chem. Commun.*, 1977, 2437.
3 D. R. Boyd and M. E. Stubbs, *J. Am. Chem. Soc.*, 1983, **105**, 2554.
4 D. R. Boyd, K. A. Dawson, G. S. Gadaginamath, J. G. Hamilton, J. F. Malone, and N. D. Sharma, *J. Chem. Soc., Perkin Trans 1*, 1981, 94.
5 D. R. Boyd, G. S. Gadaginamath, N. D. Sharma, A. F. Drake, S. F. Mason, and D. M. Jerina, *J. Chem. Soc., Perkin Trans. 1*, 1981, 2233.
6 R. N. Armstrong, B. Kedzierski, W. Levin, and D. M. Jerina, *J. Biol. Chem.*, 1981, **256**, 4726.
7 P. J. van Bladeren, R. N. Armstrong, D. Cobb, D. R. Thakker, D. E. Ryan, P. E. Thomas, N. D. Sharma, D. R. Boyd, W. Levin, and D. M. Jerina, *Biochem. Biophys. Res. Commun.*, 1982, **106**, 602.
8 S. K. Young and M. W. Chou, *Carcinogenesis*, 1980, **1**, 803.
9 K. P. Vyas, P. J. van Bladeren, D. R. Thakker, H. Yagi, J. M. Sayer, W. Levin, and D. M. Jerina, *Mol. Pharmacol.*, 1983, **24**(1), 115.
10 M. N. Akhtar, D. R. Boyd, and J. G. Hamilton, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2437.
11 D R. Boyd, G. S. Gadaginamath, A. Kher, J. F. Malone, H. Yagi, and D. M. Jerina, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2112.
12 S. K. Balani, D. R. Boyd, E. S. Cassidy, R. M. E. Greene, K. M. McCombe, and N. D. Sharma, *Tetrahedron Lett.*, 1981, 3277.
13 D. T. Gibson, V. Mahadevan, D. M. Jerina, H. Yagi, and H. J. C. Yeh, *Science*, 1975, **186**, 295.
14 D. M. Jerina, P. J. van Bladeren, H. Yagi, D. T. Gibson, V. Mahaderan, A. S. Neese, M. Koreeda, N. D. Sharma, and D. R. Boyd, *J. Org. Chem.*, 1984, in the press.

Received 31*st August* 1983; *Paper* 3/1512