# 537. ${}^{14}C$-*Labelled Polycyclic Aromatic Hydrocarbons. Part I. The Synthesis of* [9-${}^{14}$C]*Anthracene and Some Methyl-substituted Anthracenes.*

By J. R. Catch and E. A. Evans.

[9-${}^{14}$C]Anthracene and three of its monomethyl derivatives have been synthesised by a new method involving only three radiochemical steps from ${}^{14}CO_2$.

This series of papers describes syntheses of polycyclic aromatic hydrocarbons, particularly some having carcinogenic activity,[1] labelled in a ring with ${}^{14}$C, by methods which involve few radioactive stages and give good yields on a small scale, thus affording high specific activities.

[9-${}^{14}$C]Anthracene [2] was prepared by Stevens and Holland [3] from *o*-tolu[${}^{14}$C]ic acid by a six-stage synthesis, in an overall radiochemical yield of 58·5%. We describe a synthesis having only three radioactive stages, starting with the Grignard reagent from *o*-benzylbromobenzene which gave *o*-benzylbenz[${}^{14}$C]oic acid in 95% yield on carboxylation with ${}^{14}CO_2$. Ring closure of the acid with anhydrous hydrogen fluoride gave 90—99% of anthrone which on reduction with zinc dust in sodium hydroxide gave [9-${}^{14}$C]anthracene in 73·5% yield (69% based on carbon dioxide). The overall radiochemical yield from ${}^{14}CO_2$ was 72·5%. Anthrone with methylmagnesium iodide in ether–benzene gave 9-methyl[9-${}^{14}$C]anthracene in 69% overall radiochemical yield.

1-Methyl[10-${}^{14}$C]anthracene and 2-methyl[9-${}^{14}$C]anthracene were prepared similarly from the appropriate bromo-compound, in 67% and 52% overall radiochemical yield respectively from ${}^{14}CO_2$.

The bromo-compounds (1) were prepared by treating *o*-bromobenzaldehyde with the appropriate arylmagnesium bromide and reducing the resulting secondary alcohol with red phosphorus and iodine in glacial acetic acid.

*o*-Bromo-3-methylbenzylbenzene gave, on carboxylation with ${}^{14}CO_2$, a 93% yield of the acid, but cyclisation of this with anhydrous hydrogen fluoride followed by reduction of the product gave 2-methyl[10-${}^{14}$C]anthracene (chemically identical with 3-methylanthracene) in a yield of only 25%. No 1-methylanthracene was isolated, indicating the efficiency of the steric hindrance.

Small yields of anthracene, probably generally labelled with ${}^{14}$C, have been obtained by neutron bombardment of acridine,[4] together with larger amounts of labelled acridine. The yields and specific activities are, however, much too low to make this reaction a useful source of tracer compounds, and this is true of many comparable radiation syntheses of ${}^{14}$C-compounds.[5]

## Experimental

M. p.s were observed on a Kofler block and are corrected. Microanalyses were carried out by Drs. G. Weiler and F. B. Strauss, Oxford, and Mr. D. A. Lambie, Radiochemical Centre. Grignard reagents were prepared in an atmosphere of dry oxygen-free nitrogen. Radioactive samples were measured as layers of barium [${}^{14}$C]carbonate of infinite thickness, formed by burning samples in a stream of oxygen and absorbing the ${}^{14}CO_2$ in saturated aqueous barium hydroxide.

o-*Benzylbromobenzene*.—*o*-Bromobenzaldehyde (9 g.) in anhydrous ether (25 ml.) was added

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[1] Catch and Evans, *Chem. and Ind.*, 1957, 78; cf. Bhargava, Hadler, and Heidelberger, *J. Amer. Chem. Soc.*, 1955, **77**, 2877; Wiest and Heidelberger, *Cancer Res.*, 1953, **13**, 250.

[2] For previous syntheses of anthracene see " Elsevier's Encyclopædia of Organic Chemistry," Ed. Josephy and Radt, New York, 1946, Vol. XIII, p. 199.

[3] Stevens and Holland, *Science*, 1950, **112**, 718.

[4] Wolf and Anderson, *J. Amer. Chem. Soc.*, 1955, **77**, 1608.

[5] Cf. Schrodt and Libby, *ibid.*, 1956, **78**, 1267.

to phenylmagnesium bromide (from magnesium, 1·3 g., and bromobenzene, 8 g.) in ether (30 ml.). The solution was stirred at room temperature for 30 min. and then treated with excess of saturated ammonium chloride. The ether layer was separated and the aqueous layer extracted with ether (2 × 20 ml.), the ether layers were combined, and most of the solvent was removed. The residual liquid was dissolved in glacial acetic acid (150 ml.), iodine (3 g.), red phosphorus (3 g.), and water (15 ml.) were added, and the mixture was refluxed for 24 hr. When cold, the solution was filtered and ice added to the filtrate. Most of the acetic acid was neutralised with 10% aqueous sodium hydroxide and the solution extracted with ether (3 × 100 ml.). The ether extracts were washed several times with 10% aqueous sodium hydroxide and with water (2 × 100 ml.), dried ($Na_2SO_4$–$K_2CO_3$), and distilled, giving *o*-benzylbromobenzene (7·5 g., 62%), b. p. 82°/$10^{-3}$ mm., $n_D^{25}$ 1·6060 (Bergmann [6] gives b. p. 175°/22 mm.) (Found : C, 63·1; H, 4·7; Br, 31·9. Calc. for $C_{13}H_{11}Br$ : C, 63·2; H, 4·45; Br, 31·3%).

*o-Benzylbenzoic Acid*.—$^{14}CO_2$ generated from barium [$^{14}$C]carbonate (0·564 g., 1 mc) with concentrated sulphuric acid in a closed vacuum system was condensed into a Grignard solution prepared from *o*-benzylbromobenzene (0·8 g.) and magnesium (85 mg.) in ether (15 ml.). The solution was first frozen in liquid nitrogen, then held in a vacuum for 15 min., the $^{14}CO_2$ condensed in, and the solution stirred at room temperature for 30 min., refrozen, and stirred for a further 15 min. at room temperature. Water (15 ml.) and concentrated hydrochloric acid (until acid) were added, the ether layer separated, and the aqueous layer extracted with ether (3 × 20 ml.). The combined ether layers were extracted with 2N-sodium hydroxide (4 × 25 ml.), and the alkaline extracts acidified with concentrated hydrochloric acid. After slow cooling to 0° the crude labelled *o*-benzylbenzoic acid was filtered off (m. p. 108—111°); it crystallised in needles (0·57 g., 95%) (*a*) from aqueous ethanol (m. p. 114°), which were pure enough for the next stage. A sample crystallised to constant m. p. had m. p. 115—116° (lit.,[7] m. p. 117°). To the mother-liquors was added inactive carrier *o*-benzylbenzoic acid (200 mg.) and on concentration and crystallisation more acid (270 mg.), m. p. 108—110° (*b*), was obtained.

[9-$^{14}$C]*Anthrone*.—*o*-Benzylbenzoic acid (570 mg., *a* above) was treated in a platinum crucible with anhydrous fluoride (*ca.* 8—10 ml.), left at room temperature for 10 min. with occasional stirring, and then poured on ice. The anthrone (470 mg., 90%), m. p. 154—155° (Fieser and Hershberg [8] give m. p. 154—156°), was filtered off. Cyclisation of *o*-benzylbenzoic acid (220 mg., *b*) gave anthrone (200 mg., 99%). In other experiments yields between 90 and 99% were obtained.

[9-$^{14}$C]*Anthracene*.—Anthrone (150 mg., prepared from acid *a*) was refluxed with zinc dust (1 g.) (activated by copper sulphate), 2N-sodium hydroxide (10 ml.), and toluene (5 ml.) for 3 hr. The toluene layer was separated, the aqueous layer extracted with benzene (3 × 5 ml.), and the excess of zinc dust washed with hot benzene (3 × 5 ml.). The combined extract and washings were dried ($Na_2SO_4$), and the solvents removed. The residual solid crystallised from toluene, giving [9-$^{14}$C]anthracene (100 mg., 73·5%), m. p. and mixed m. p. 214—215° (Baxter and Hale [9] give m. p. 216·2—216·4°), 400 μc/mmole. Reduction of anthrone (200 mg.) prepared from acid *b* gave anthracene (75 mg.), m. p. 215°, 48·6 μc/mmole.

*9-Methyl*[9-$^{14}$C]*anthracene*.—Anthrone (100 mg.) from acid *a* in benzene (5 ml.) was added to methylmagnesium iodide (from magnesium, 72 mg., and methyl iodide, 430 mg.) in ether (10 ml.). The mixture was refluxed for 3—4 hr., then cooled, and excess of hydrochloric acid (50% v/v) was added. The organic layer was separated and the aqueous layer extracted with benzene (2 × 10 ml.). The combined organic layers were dried ($Na_2SO_4$) and evaporated under reduced pressure. The residual solid crystallised from aqueous ethanol, to give 9-methyl-[9-$^{14}$C]anthracene (68 mg., 70%), m. p. 77—79°, 414 μc/mmole. After two recrystallisations a sample of m. p. and mixed m. p. 78—79° was obtained (Sieglitz and Marx [10] give m. p. 81·5°).

*o-Bromo-2-methylbenzylbenzene*.—*o*-Bromobenzaldehyde (5 g.) in ether (25 ml.) was added dropwise to *o*-tolymagnesium bromide (from magnesium, 0·72 g., and *o*-bromotoluene, 5 g.) in ether (25 ml.). Isolation of the secondary alcohol and reduction with phosphorus (2 g.) and iodine (2 g.) as above gave *o-bromo-2-methylbenzylbenzene* (5·0 g., 71%), b. p. 105°/$10^{-2}$ mm., $n_D^{19}$ 1·6047 (Found : C, 63·8; H, 5·0; Br, 30·5. $C_{14}H_{13}Br$ requires C, 64·4; H, 5·0; Br, 30·6%).

*o-2-Methylbenzylbenz*[$^{14}$C]*oic Acid*.—$^{14}CO_2$ (from barium[$^{14}$C]carbonate, 0·985 g., 150 μc)

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[6] Bergmann, *J. Org. Chem.*, 1939, **4**, 1.

[7] Fischer and Schmidt, *Ber.*, 1894, **27**, 2788.

[8] Fieser and Hershberg, *J. Amer. Chem. Soc.*, 1939, **61**, 1272.

[9] Baxter and Hale, *ibid.*, 1937, **59**, 506.

[10] Sieglitz and Marx, *Ber.*, 1923, **56**, 1619.

was condensed into the Grignard reagent from *o*-bromo-2-methylbenzylbenzene (1·85 g.), magnesium (0·18 g.), and iodine (1 crystal) in a closed vacuum-system. Isolation of the acid as above gave *o*-2-methylbenzylbenz[$^{14}$C]oic acid (1·2 g., 100%), m. p. 116—119°, which was used for the next stage without further purification. A sample crystallised in plates from aqueous ethanol had m. p. and mixed m. p. 125—126° (Bergmann and Loewenthal[11] give m. p. 128—130°).

1-*Methyl*[10-$^{14}$C]*anthracene*.—*o*-2-Methylbenzylbenz[$^{14}$C]oic acid (1·2 g.) was stirred in anhydrous hydrogen fluoride (30 ml.) for 30 min. The cyclised product, isolated as above, was reduced under reflux for 6 hr. with zinc dust (5 g.), 5N-sodium hydroxide (50 ml.), and toluene (25 ml.). Isolation as for anthracene gave 1-methylanthracene (0·62 g.), m. p. 83—84°, which after one crystallisation from methanol (charcoal) gave colourless needles (0·57 g.), 31 $\mu$c/mmole, m. p. 84—85° (Fischer and Sapper[12] give m. p. 85—86°).

o-*Bromo*-4-*methylbenzylbenzene*.—This *compound*, prepared in 64% yield from *o*-bromobenzaldehyde (5 g.) and *p*-tolylmagnesium bromide, as above, had b. p. 103—104°/10$^{-4}$ mm., $n_D^{20}$ 1·6002 (Found: C, 64·7; H, 5·3; Br, 29·7%).

o-4-*Methylbenzylbenz*[$^{14}$C]*oic Acid*.—Prepared quantitatively from $^{14}CO_2$ (5 mmole, 150 $\mu$c) and the Grignard reagent from *o*-bromo-4-methylbenzylbenzene, this acid had m. p. 127—129°. A sample recrystallised from aqueous ethanol had m. p. and mixed m. p. 130—131° (Found: C, 80·2; H, 6·6. Calc. for $C_{15}H_{14}O_2$: C, 79·7; H, 6·2%) (Bergmann and Loewenthal[11] give m. p. 133·5—134°).

2-*Methyl*[9-$^{14}$C]*anthracene*.—Cyclisation of the preceding acid (1·2 g.) and reduction as above gave 2-methyl[9-$^{14}$C]anthracene (0·6 g.) which was isolated by sublimation *in vacuo* and crystallised from methanol in plates (0·5 g., 52% from $^{14}CO_2$), m. p. and mixed m. p. 204—205° (lit.,[13] 207°), 30 $\mu$c/mmole (Found: C, 93·6; H, 6·3. Calc. for $C_{15}H_{12}$: C, 93·7; H, 6·3%). No significant amounts of acid were recovered from the aqueous alkaline layer after the reduction.

o-*Bromo*-3-*methylbenzylbenzene*.—Prepared from *o*-bromobenzaldehyde (4 g.) and *m*-tolylmagnesium bromide, as above, this *compound* (3·8 g., 67%) had b. p. 103—104°/10$^{-3}$ mm., $n_D^{20}$ 1·6016 (Found: C, 65·1; H, 4·9; Br, 29·9%).

o-3-*Methylbenzylbenz*[$^{14}$C]*oic Acid*.—Prepared from $^{14}CO_2$ (5 mmole, 150 $\mu$c) and the appropriate Grignard reagent in 93% yield, the *acid* crystallised from aqueous ethanol in plates, m. p. and mixed m. p. 101—102° (Found: C, 79·5; H, 6·3%).

2-*Methyl*[10-$^{14}$C]*anthracene*.—Cyclisation of the preceding acid and reduction of the product gave, after chromatography of the hydrocarbons on alumina in benzene and crystallisation from methanol, 2-methyl[10-$^{14}$C]anthracene (250 mg., 25%), m. p. and mixed m. p. 204—205°, 30 $\mu$c/mmole. No other identifiable products were isolated.

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[11] Bergmann and Loewenthal, *Bull. Soc. chim. France*, 1952, **19**, 66.

[12] Fischer and Sapper, *J. prakt. Chem.*, 1911, **83**, 203; Keimatsu, Hirano, and Yoshimi, *J. Pharm. Soc. Japan*, 1930, **50**, 644.

[13] Fischer, *J. prakt. Chem.*, 1909, **79**, 555; Scholl and Lenko, *Monatsh*, 1918, **39**, 237.