601. *Synthesis of* 2-[8-^{14}C]*Naphthylamine.*

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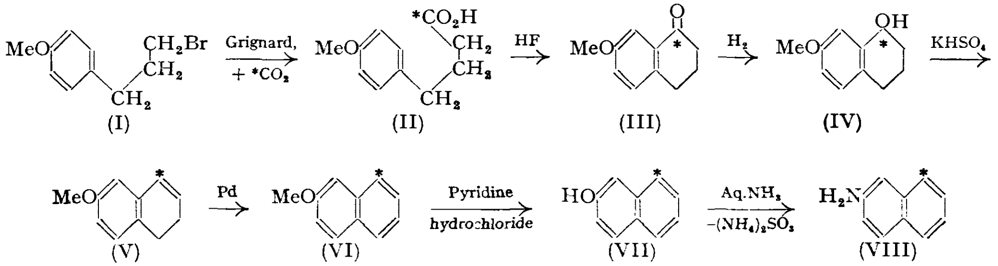
2-Naphthylamine labelled with ^{14}C in position 8 has been synthesized with a specific activity of about 2·5 mc./millimole. [1-^{14}C]Naphthalene is produced as a by-product.

2-NAPHTHYLAMINE labelled with ^{14}C was required for an investigation of its mode of action as a bladder carcinogen. It was synthesized by the reactions formulated.

Direct reduction of (III) to the tetralin was slow and uncertain and dehydrogenation of the latter produced up to 40% of naphthalene as well as (VI). It was more satisfactory to proceed by way of (IV) and (V) as shown though the hydrogenation was still erratic and was not improved by recrystallizing the tetralone. The product from dehydrogenation of (V) was distilled, to give a mixture of naphthalene and (VI), which was treated with



pyridine hydrochloride to hydrolyse the methoxy-compound to the naphthol, which was then extracted with alkali.

The naphthylamine was purified by repeated sublimation from silica, a method developed for larger-scale work by Dr. R. A. M. Case and shown by him to produce very pure material from commercial naphthylamine (personal communication). The purified naphthylamine is sensitive to light and oxygen, but in their absence has been kept unchanged for 18 months.

Animal experiments with 2-[8-^{14}C]naphthylamine will be reported elsewhere.

EXPERIMENTAL

3-p-*Methoxyphenylpropyl Bromide.*—(*a*) Ethyl *p*-methoxycinnamate was prepared from anisaldehyde and ethyl acetate in ether in the presence of sodium as described by Horeau (*Bull. Soc. chim.*, 1948, **15**, 414) except that the sodium was powdered by stirring it under toluene, excess of toluene being removed by decantation. Yields of 73% on anisaldehyde were obtained. The ethyl *p*-methoxycinnamate had b. p. 184—187°/16 mm.

(*b*) Ethyl *p*-methoxycinnamate (226 g.) in ethanol (1 l.) was shaken with hydrogen at room temperature and atmospheric pressure in presence of palladized barium sulphate (2%; 1 g.). Reduction was complete (absorption, 25 l.) in about 16 hr., three further additions of catalyst being necessary. Filtration, evaporation, and distillation under reduced pressure gave ethyl β-*p*-methoxyphenylpropionate (218 g., 95%), b. p. 160—168°/18 mm.

No hydrogenation took place over a catalyst of (not recently prepared) Raney nickel.

(*c*) Ethyl β-*p*-methoxyphenylpropionate (218 g.) in ether was added with stirring to lithium aluminium hydride (25 g.) in boiling ether, excess of hydride decomposed by ethyl acetate, water and dilute hydrochloric acid were added, and the ethereal layer was dried and evaporated. Distillation of the residue gave 3-*p*-methoxyphenylpropan-1-ol (152 g., 87%), b. p. 164—168°/18 mm., which largely crystallized at room temperature (lit., m. p. 26°).

Direct reduction of ethyl *p*-methoxycinnamate with lithium aluminium hydride under similar conditions gave only 3-*p*-methoxyphenylprop-2-en-1-ol in 37% yield. The reduction with sodium in amyl alcohol used by Horeau was found to be very sensitive to traces of water and the above two-stage method gave better yields.

(*d*) 3-*p*-Methoxyphenylpropyl bromide was prepared in 67% yield as described by Horeau (*loc. cit.*) from the alcohol and phosphorus tribromide in carbon tetrachloride at 60—70°. Increasing the proportion of phosphorus tribromide or the reaction time did not improve the yield. The compound did not interact with magnesium in ether alone, but after initiation with methyl iodide a moderate reaction took place. For purification the bromide (81 g.) was distilled through a 4″ column packed with glass rings, to give fractions: (1) b. p. 150—163°/22 mm. (1 g.), 97% pure on bromine content, somewhat discoloured; (2) b. p. 163—166°/22 mm. (66 g.), 100% pure, colourless; (3) residue (12 g.), 93% pure on bromine content.

A " tracer " run with $^{14}CO_2$ of low activity was now carried out as follows:

4-p-*Methoxyphenylbutan*[^{14}C]*oic Acid.*—3-*p*-Methoxyphenylpropyl bromide (900 mg.), magnesium turnings (110 mg.), and a crystal of iodine were refluxed in dry ether (5 c.c.) for 1 hr. The Grignard solution thus obtained was frozen in liquid nitrogen, the flask connected to a vacuum system and evacuated, and $^{14}CO_2$ (2·65 millimoles, 38,000 c.p.m./millimole) condensed into it. After warming to room temperature and storage for 1½ hr. with occasional shaking, the mixture was decomposed with ice and dilute sulphuric acid in a separating funnel (fitted with mechanical stirring), and the acid extracted from the ethereal layer with sodium carbonate solution. After being washed with ether, the sodium carbonate solution was acidified and extracted with ether, and the acid obtained by evaporating this ethereal extract was sufficiently pure for the next stage. The yield was 493 mg. (95%). In larger runs of 13—14 millimoles the yields were 90—91%.

7-*Methoxy*-1-[1-^{14}C]*tetralone* (cf. Campbell and Todd, *J. Amer. Chem. Soc.*, 1942, **64**, 934).—The ethereal solution of β-*p*-methoxyphenylbutanoic acid obtained above was evaporated in a " Polythene " tube, and the residue dissolved in anhydrous hydrogen fluoride (*ca.* 5 c.c.) and kept overnight in the stoppered tube. Most of the hydrogen fluoride was then allowed to evaporate, and the remainder neutralized with solid sodium carbonate. The ketone was extracted with ether and washed with sodium carbonate solution. Evaporation of the ether gave yellow crystals (403 mg., 90%) which were dissolved in ethereal diazomethane and set aside for a few min. to methylate any free phenol. The solution was evaporated and the residue used directly for the next stage.

2-*Methoxy*[8-^{14}C]*naphthalene*.—7-Methoxytetralone was hydrogenated in methanol over palladium black (50 mg.) with magnetic stirring. Uptake was very slow, and addition of fresh catalyst was often necessary. After the uptake of about 1 mol. of hydrogen, the solution was filtered and evaporated, and the residue heated with freshly fused potassium hydrogen sulphate (300 mg.) at 200° for 2 hr. The melt was then extracted with ether, which was washed with water, dried, and evaporated, and fresh palladium black (50 mg.) was added to the residue. A deep blue colour was immediately produced, which however disappeared at 200—230°. After 2½ hr. at this temperature the residue was distilled at *ca.* 60°/10^{-2} mm. The distillate (288 mg.) solidified incompletely, probably owing to the presence of naphthalene, which was not separated at this stage.

2-[8-^{14}C]*Naphthylamine*.—The distillate obtained above was heated with 10 times its weight of pyridine hydrochloride (commercial, containing some pyridine which is desirable for washing sublimed material out of the condenser) at 200° for 6 hr. (cf. Prey, *Ber.*, 1941, **74**, 1219). The melt was taken up in ether and washed with dilute hydrochloric acid, and the naphthol extracted with sodium hydroxide solution, giving 135 mg. of alkali-soluble material; 137 mg. were recovered from the ether, and naphthalene was isolated therefrom by sublimation (m. p. 76—79°; picrate, m. p. 149—150°). Further purification by chromatography on alumina and recrystallization from alcohol gave material of m. p. 79·5°.

The crude naphthol was transferred to a " Pyrex " tube (*ca.* 20 × 200 mm.), which was then half filled with a mixture of equal parts of aqueous ammonia (*d* 0·880) and freshly prepared ammonium sulphite solution, sealed, and heated at 150° for 17 hr. On cooling, the mixture was extracted with ether, which was washed with water and extracted with dilute hydrochloric acid, to afford the naphthylamine (101 mg., crude; 26·5% from $^{14}CO_2$).

In the high-activity run, 27·2 millimoles of $^{14}CO_2$ (2·51 mc./millimole) were used. 3·24 millimoles (13%) of the acid (II) were recovered from the hydrogen fluoride cyclization, and 1·37 millimoles (5%) of 2-naphthol were removed for purification. The yield of naphthylamine was 4·4 (16%) and of naphthalene 1·52 millimoles (5·6%).

For radioactive assay the products were diluted with pure carrier material. The naphthol and naphthylamine were also converted into their acetyl derivatives which were purified and assayed similarly. All measurements were by combustion in the dry way and end-window counting of infinitely thick films in standard geometry. The values, calculated to the provisional standard of the National Bureau of Standards, were as follows (mc./millimole): 2-naphthol (crude) 2·44; 2-naphthyl acetate (pure) 2·40; 2-naphthylamine (crude) 2·52; acetonaphthylamide (pure) 2·48; naphthalene, crude 2·51, pure 2·69.

The naphthylamine (after purification by the method described below) was also assayed by a gas counting method. Three samples of the amine were burnt in a standard microanalytical combustion tube and the gases collected by freezing in liquid nitrogen. The carbon dioxide was then freed from water by evaporation from a solid carbon dioxide–acetone bath, and after dilution with inactive carbon dioxide an aliquot was counted in a CO_2–CS_2 gas counting tube (cf. A. F. Henson, *Brit. J. Appl. Phys.*, 1953, **4**, 217). The values obtained were: 2·988 × 10^7, 3·028 × 10^7, 2·937 × 10^7 c.p.m./mg. (mean 2·984 ± 0·027 × 10^7). The efficiency of the counters (72%) was measured by oxidizing samples of standard labelled " Perspex " and counting the carbon dioxide formed. This correction being made, the specific activity of the naphthylamine is 2·67 mc./millimole.

Purification of 2-[8-^{14}C]*Naphthylamine*.—Naphthylamine and 10% (wt.) of silica (100—200 mesh) were introduced into a long tube having several constrictions. The amine was sublimed (80—95°/10^{-6} mm.) beyond the first constriction, which was sealed off, and the amine sublimed twice more to ensure the removal of silica. The product still had a faint creamy tinge, so the process was repeated, yielding a pure white compound, m. p. 108·4—109·9°.

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