THE PREPARATION OF [^{15}N]- AND [1-^{13}C]-2-NAPHTHYLAMINE AND THEIR CONVERSIONS INTO [^{15}N,^{15}N']- AND [1,1'-$^{13}C_2$]-2,2'-AZONAPHTHALENE

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ABSTRACT

Specifically labelled [^{15}N]-2-naphthylamine and [1-^{13}C]-2-naphthylamine have been synthesized with approx. 99% label abundance. The correspondingly highly-enriched, doubly-labelled 2,2'-azonaphthalenes have been made.

Key Words: [^{15}N]- and [1-^{13}C]-2-naphthylamine. Doubly labelled 2,2'-azonaphthalenes.

INTRODUCTION

Specifically labelled ^{15}N- and ^{13}C-2,2'-azonaphthalene were needed for studying the mechanism of rearrangement of 2,2'-hydrazonaphthalene. 2,2'-Azonaphthalene can be prepared in reasonable yield only by the diazotized coupling of 2-naphthylamine. Hence it was necessary first to prepare specifically labelled [^{15}N]- and [1-^{13}C]-2-naphthylamine. The former has been prepared by Geller and Samosvat (1), and we adapted their sealed-tube procedure to our own needs.

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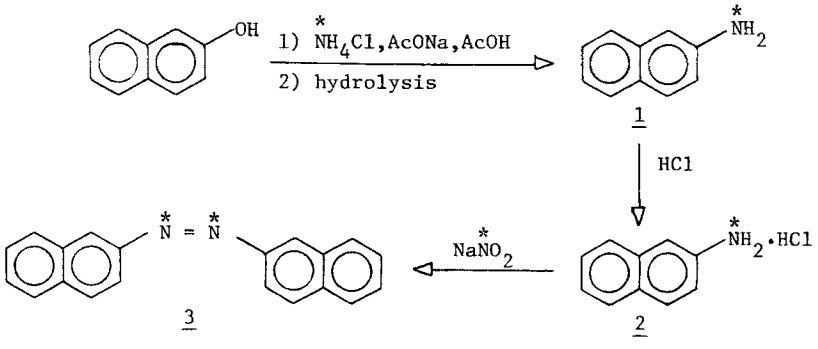
2-Naphthylamine has been prepared with ^{13}C-labelling in the 8- and 1,4,5,8-positions (2). $[^{13}C_2]$-5,8-$[^{1}H_4]$-5,6,7,8-tetrahydro-2-naphthylamine has also been reported (3). 2-Naphthylamine having ^{14}C-labelling in the 8- (4) and 5,8- (5) positions has been reported also. To our knowledge 2-naphthylamine which is specifically labelled in the 1-position has not been reported hitherto.

EXPERIMENTAL

$[^{15}N]$-2-Naphthylamine and $[^{15}N,^{15}N']$-2,2'-Azonaphthalene (Scheme 1).

$[^{15}N]$-2-Naphthylamine. The sealed-tube procedure of Geller (1) was modified. A glass-lined autoclave (Parr "Mini" reactor) was charged with 3.0 g (0.02 mol) of 2-naphthol, 4.8 g (0.09 mol) of $[^{15}N]$ammonium chloride (99% ^{15}N), 8.2 g of anhydrous sodium acetate, and 3.0 mL of glacial acetic acid. The mixture in the autoclave was heated for 10 h at 280° C. After cooling, the autoclave was opened, the contents were washed out with water into a suction filter and the solid residue was washed with water until a test for chloride ion was negative (filtrate 1). The residue was then refluxed in 200 mL of 1.2% aqueous sodium hydroxide for 1 h. The alkaline solution was cooled in ice, the insoluble solid was filtered and washed 3 times with ice water (filtrate 2), and then refluxed with 200 mL of 6% hydrochloric acid for 1 h. The hot solution was filtered (filtrate 3). Filtrate 2 was extracted

SCHEME 1



5 times with ether. The extract, containing a little [^{15}N]-2-napthylamine, was added to filtrate 3, which was then made alkaline with 20 g of sodium hydroxide. The ether was distilled off and then the [^{15}N]-2-naphthylamine was steam distilled. The distillate was extracted with ether, the extract was dried with solid sodium hydroxide, and the ether solvent was evaporated to leave 1.1 - 1.2 g (37-40%) of slightly colored, crystalline [^{15}N]-2-naphthylamine, mp 108-110° C.

Regeneration of [^{15}N]ammonium chloride. Filtrate 1 was transferred to a flask and made alkaline with 10 g of sodium hydroxide. The ammonia was distilled off with steam into a receiver containing 6 mL of concentrated hydrochloric acid diluted with 25 mL of water. Completion of distillation was detected by hydrion paper placed at the exit of the condenser. Evaporation of the acidic distillate, and washing the dried residue with acetone left 2.4 - 2.6 g of [^{15}N]ammonium chloride.

[^{15}N]-2-Naphthylamine hydrochloride. (2). [^{15}N]-2-Naphthylamine (3.3 g, 0.023 mol) was dissolved in 150 mL of boiling hydrochloric acid (50% by volume). The solution was decolorized by boiling with charcoal, and filtered while hot. Colorless crystals of [^{15}N]-2-naphthylamine hydrochloride deposited upon cooling. The product was filtered and allowed to dry, giving 3.8 g (93%) of [^{15}N]-2-naphthylamine hydrochloride, mp 245-247° C.

[^{15}N,^{15}N']-2,2'-Azonaphthalene (3). The method of coupling 2-naphthylamine by Cohen and Oesper (6) was adapted and partly modified for ^{15}N labelling. [^{15}N]-2-naphthylamine hydrochloride (3.6 g, 0.02 mol) was stirred into 50 mL of water. To this was added 1.8 mL of concentrated hydrochloric acid and the solution was cooled to 0° C in an ice-salt bath while being stirred with a magnetic stirrer. After adding 2.2 mL of concentrated sulfuric acid in 21 mL of water, the suspended amine salt was stirred vigorously and diazotized by slowly adding, below the surface, a cold solution of 1.44 g of sodium [^{15}N]nitrite, (99% ^{15}N). The reddish brown solution of the diazonium salt was allowed

to stand 15 min and was then filtered by suction, the filtrate being received in a filter flask standing in an ice bath. The cold solution was transferred to a beaker in an ice bath and a cold solution of 6.8 g of anhydrous sodium acetate in 30 mL of water was added while the system was kept between 0-5° C. A cooled solution of 3.2 g of sodium sulfite in 20 mL of water was slowly added below the surface causing nitrogen evolution and the separation of the crude [^{15}N,^{15}N']-2,2'-azonaphthalene. After addition was complete, the mixture was stirred for 15 min, removed from the ice-salt bath and 15 mL of ether was added to induce coagulation. The precipitate was filtered off after over-night standing, washed, and dried in vacuo over calcium chloride. The crude product was crystallized from benzene, giving 2.0 g (71%) of [^{15}N,^{15}N']-2,2'-azonaphthalene, mp 206.5-208° C. Mass spectrometric analysis of the product (7) gave 99.4% $^{15}N_2$ and 0.80% $^{15}N_1$.

[1-^{13}C]-2-Naphthylamine and [1,1-$^{13}C_2$]-2,2'-Azonaphthalene (Scheme 2).

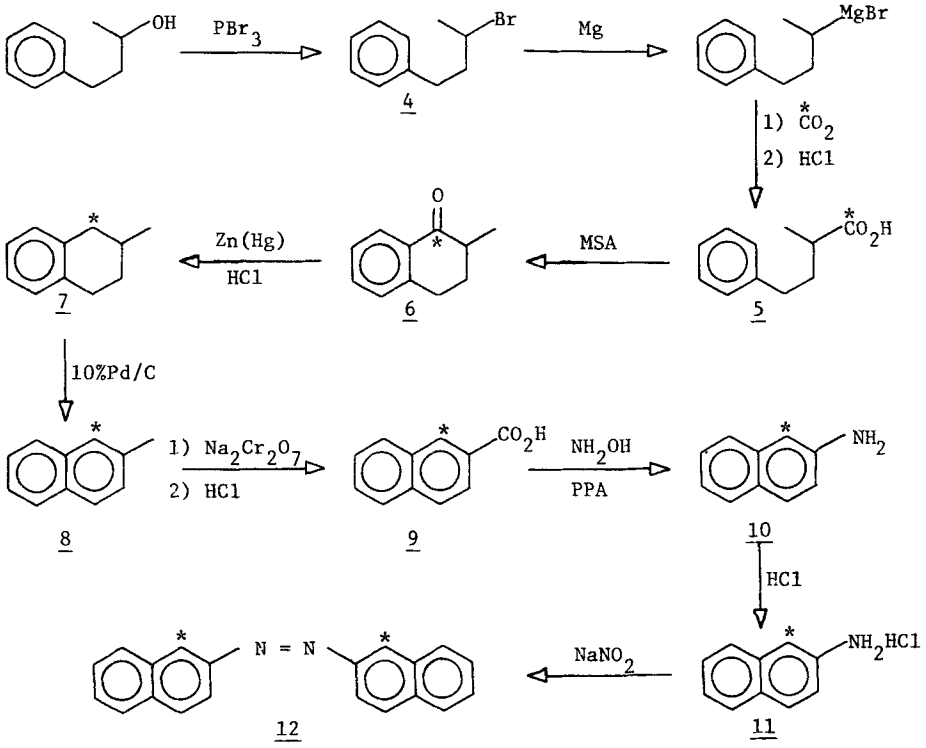
2-Bromo-4-phenylbutane (4). The procedure used was adapted from the analogous preparation of 1-bromo-2-methyl-3-phenylpropane (8). Phosphorus tribromide (76 g, 0.281 mol) was slowly added dropwise with stirring to 40 g (0.266 mol) of 4-phenylbutan-2-ol (Aldrich, 98%, used without further treatment) at 0°C. After standing 40 h at 0°C and 3 h at room temperature the mixture was heated at 90-100°C for 3 h, cooled and poured onto crushed ice. Extraction with ether and work up gave 52 g (92%) of product which was distilled to give 50 g (88%) of 4, bp 160-161°C (22 mm Hg).

[1-^{13}C]-2-Methyl-4-phenylbutanoic acid (5). Grignard reagent in excess was made by heating under gentle reflux for 4 h 1.5 g (62.3 mmol) of magnesium turnings and 12.5 g (58.7 mmol) of 4 in 90 mL of dry ether. After adding a further 50 mL of ether the Grignard solution was carbonated on a vacuum manifold using the freeze-thaw procedure described by Dauben et al. (9). [^{13}C]-carbon dioxide was generated from 4.26 g (21.6 mmol) of barium [^{13}C]carbonate,

(99% enriched, Stohler Isotopes) and 32 mL of sulfuric acid, and was carried into the Grignard solution through a drying tube by gentle nitrogen flow. The Grignard solution was stirred magnetically at -20°C during 30 min. After being frozen again in liquid N_2 the reaction mixture was allowed to stand at room temperature for 10 h before being acidified with dilute HCl and worked up. The ether extracts were combined and extracted with 10% aqueous NaOH solution, which after acidification and extraction with ether gave 3.36 g (18.8 mmol, 87% based on $Ba^{13}CO_3$) of 5. This procedure was repeated several times in order to obtain a sufficient amount of 5 for further use. The product was used without distilling it first.

[1-^{13}C]-2-Methyl-1-tetralone (6). Cyclization of 5 (12.3 g, 68.7 mmol) was achieved by heating in 90 mL of methanesulfonic acid for 3 h as described by Eisenbraun for unlabeled 6 (10). This gave 10.8 g (67.3 mmol, 98%) of 6,

SCHEME 2



[1-^{13}C]-2-Methylnaphthalene (8). Reduction of 6 to [1-^{13}C]-2-methyltetralin (7) was carried out by the general procedure in Fieser and Fieser (11). To do this, 100 g of Zn dust was amalgamated by shaking with 8 g of $HgCl_2$ and 5 mL of conc. HCl in 100 mL of water. Reduction of 10.5 g (65.2 mmol) of 6 was achieved by stirring and refluxing with the amalgamated Zn in a mixture of 40 mL of water, 90 mL of toluene, 125 mL of conc. HCl and 5 mL of acetic acid. Three 40-mL portions of conc. HCl were added at 9-h intervals during the reflux period. Ether extracts of the aqueous layer were combined with the toluene layer and gave 9.4 g of 7 as a golden yellow oil. This was dehydrogenated without further treatment by heating with 2 g of 10% palladium on charcoal at 280°C for 30 h. Extraction with ether and removal of the solvent gave 7.78 g (54.4 mmol, 83% based on 6) of 8, mp 30-32°C. Lit. mp 34.5°C (8).

[1-^{13}C]-2-Naphthoic acid (9). Oxidation of 8 with aqueous $Na_2Cr_2O_7$ was carried out with the method of Friedman (12). For this purpose a mixture of 7.49 g (51.7 mmol) of 8, 24.1 g (80.8 mmol) of $Na_2Cr_2O_7$, and 42 mL of water was heated in the Parr autoclave for 25 h at 250°C. The autoclave contents were removed and filtered at 60°C. The filter residue was washed with 1300 mL of warm water, and the combined aqueous solution was acidified with 1:1 hydrochloric acid and cooled overnight to give 7.02 g (40.6 mmol, 78%) of 9, mp 183-184°C (from ethanol). Lit. yield and mp for unlabeled 9 were 93% and 184-185°C (12).

[1-^{13}C]-2-Naphthylamine (10). Conversion of 9 into 10 was carried out by heating a mixture of 2.10 g (30 mmol) of hydroxylamine hydrochloride, 2.58 g (15 mmol) of 9, and 38 g of polyphosphoric acid (Aldrich) as described by Snyder (13). Control runs showed that good conversions could be obtained only if reasonably fresh polyphosphoric acid was used. Polyphosphoric acid which had been kept for some time after part had been used gave low yields of 2-naphthylamine. Work up gave 1.5 g (11 mmol, 74%) of dark-colored 10, mp 102-105°C. Lit. mp 107-109°C (unlabeled) (13). The 10 was purified as its hydrochloride (11), mp 251-253°C, which was used for preparing the azo compound (12).

[1,1'-$^{13}C_2$]-2,2'-Azonaphthalene (12) was prepared in 70% yield by the procedure described for [^{15}N,$^{15}N'$]-2,2'-azonaphthalene, above.

Mass spectrometric analysis of the 12 (7) gave: 95.2% $^{13}C_2$, 4.27% $^{13}C_1$ and 0.50% $^{13}C_o$. After each step in the syntheses above, the structure of the product was checked by ^1H NMR and IR spectroscopy. TLC was used to confirm the absence of mixtures.

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