DEUTERATED ORGANIC COMPOUNDS

XXII. SYNTHESIS OF SOME DEUTERATED BENZENE DERIVATIVES[1]

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ABSTRACT

The deamination of certain aromatic amines in deuterohypophosphorous acid with sodium or isoamyl nitrite has been used to label aromatic compounds in a specific position with deuterium. Aniline 2,3-d_2 was synthesized by this method.

Exchange with deuterium sulphate has been extended to the deuteration of nitrotoluenes, bromotoluenes, and polychlorobenzenes.

Previous communications in this series (1, 2, 3) have dealt very largely with the synthesis of deuterated aliphatic compounds. Aromatic compounds were investigated only incidentally and then interest was centered on introducing deuterium into the side chain rather than into the nucleus. In this paper the deuteration of aromatic compounds will be formally discussed.

The total replacement of hydrogen by deuterium in the aromatic series is in general effected more readily than in aliphatic compounds. Some years ago one of us (4) showed that benzene-d_6 could be conveniently prepared by exchange with deuterium oxide at 100° C in the presence of platinum black. Others (5, 6, 7) have since reported that benzene derivatives such as benzoic acid or aniline and polynuclear hydrocarbons can be deuterated as well. In contrast, alkanes undergo exchange under these conditions only when deuterium gas is also present.

The exchange with deuterium oxide catalyzed by platinum black yields compounds completely deuterated in the ring. The method is therefore inapplicable for the preparation of compounds containing deuterium in specific positions. Several methods of obtaining such compounds have, however, been investigated in the past.

In early attempts to prepare deuterated benzenes, calcium salts of aromatic acids were decarboxylated in the presence of calcium deuteroxide. Morita and Titani (8) prepared benzene-d_1 by this method from anhydrous calcium benzoate. Later, Redlich and Stricks (9) obtained benzene-1,2-d_2 from calcium phthalate and Weldon and Wilson (10) synthesized benzene-1,3,5-d_3 from the calcium salt of mesitylene carboxylic acid. Finally, Erlenmeyer carried the method to its logical conclusion by preparing benzene-d_6 from calcium mellitate (11). The reaction was later reinvestigated by Best and Wilson (12), who showed that the isotopic purity of the products was low due to exchange under the drastic conditions employed.

Another method of obtaining deuterated benzenes is the hydrolysis of Grignard reagents with deuterium oxide or deuterium chloride. However, only one atom of deuterium can usually be introduced in this way. Redlich and Stricks (13) had prepared benzene-1,2-d_2 from 1,2-diiodobenzene in this manner but later work by Best and Wilson (12) showed the dimagnesium reagent from 1,4-dibromobenzene exchanged with ether presumably by a free radical mechanism to give benzene-1,4-d_2 of low isotopic purity. They circumvented this difficulty by introducing the deuterium in two stages, i.e. by two separate Grignard preparations and hydrolyses. In any event the application of Grignard

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[1] *Manuscript received August 19, 1960.*
Contribution from the Division of Pure Chemistry, National Research Council, Ottawa, Canada. Presented at the 43rd Conference of the Chemical Institute of Canada, Ottawa, June, 1960.
Issued as N.R.C. No. 6046.
[2] *Terminated May, 1959.*

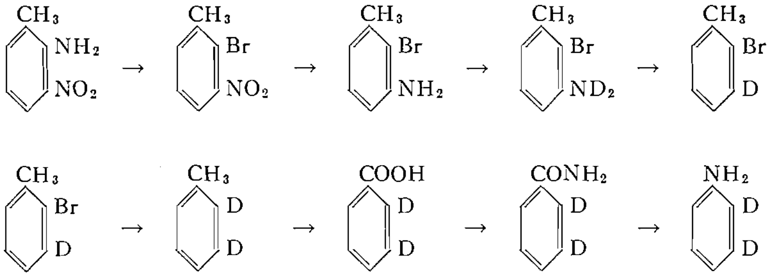
Can. J. Chem. Vol. 39 (1961)

reagents to the problem of deuteration is severely restricted by the incompatibility of organometallic halides with several other functional groups such as nitro, carboxyl, amino, etc. Nevertheless, the Grignard synthesis is probably the best method of preparing benzene-d_1, the three deuterated toluenes, and perhaps other deuterated alkyl benzenes.

Deamination is a well-known method of replacing an amino group by hydrogen (14). It is usually carried out by heating the diazonium salt of the amine in ethanol. The mechanism of this reaction has recently been shown by deTar and Turetzky (15) to be a free radical process. It is not attractive for replacing an amino group by deuterium because ethyl alcohol labelled with deuterium on the methylene group is required. In the present work deamination in isopropyl alcohol was investigated since isopropyl-2-*d* alcohol, $CH_3CD(OH)CH_3$, is easily prepared from acetone and lithium aluminum deuteride. However, the yields obtained in the decomposition of the diazonium fluoborate in isopropyl alcohol were very poor and the method was abandoned in favor of deamination in hypophosphorous acid.

In conventional deamination with hypophosphorous acid (16) the amine is first diazotized in hydrochloric or sulphuric acid and the solution of the diazonium salt is treated with an excess of 50% hypophosphorous acid. Since preparation of diazonium salts in deuterium oxide as solvent is prohibitive on economic grounds, it was decided to deaminate some representative amines directly in 50% hypophosphorous acid solutions by addition of sodium nitrite. It was felt hypophosphorous acid would be strong enough to allow diazotization to take place. This was indeed found to be the case. Bromobenzene was obtained in 70% yield from 2-bromoaniline. A search of the literature revealed only one case of diazotization in H_3PO_2, Henry and Finnegan (17) having deaminated 5-aminotetrazole in 5% hypophosphorous acid. In the present work 2-bromo-3-methylaniline, 1-naphthylamine, and pentachloroaniline were similarly deaminated in 50% hypophosphorous acid.

The replacement of NH_2 by deuterium by the above method was an important step in a synthesis of aniline-2,3-d_2 which was required in connection with some work in N.M.R. spectroscopy (18). The most feasible route to this compound appeared to be the sequence of reactions shown below:



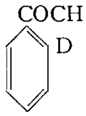
The preparation of the starting compound, 3-nitro-2-aminotoluene, has been reported in *Organic syntheses* (19). The amino group was replaced by bromine by a Sandmeyer reaction. The nitro group was successfully reduced to amino without simultaneous loss of bromine by reduction with activated iron powder in dioxane as described by Hazlett and Dornfeld (20). Deamination in hypophosphorous acid containing a low concentration of deuterium has been shown to be subject to a high deuterium isotope effect in favor of hydrogen (21). This meant that rigorous exclusion of exchangeable hydrogen was absolutely necessary to obtain a high concentration of deuterium in the product. Consequently, hypophosphorous acid was exchanged with deuterium oxide as described by Hammond and Grundemeier (22) until the hydrogen atom signal in the N.M.R. spectrum was absent. Similarly the hydrogen in the amino group of the amine was replaced by deuterium by several exchanges in slightly alkaline deuterium oxide. The 2-bromotoluene-3*d* isolated in 50% yield was 96 mole% C_7H_6BrD. The second deuterium atom was introduced via a Grignard synthesis. The deuterium content of the toluene-2,3-d_2 was 83 mole %. It was oxidized to benzoic-2,3-d_2 acid in aqueous alkaline permanganate without loss of deuterium. Aniline-2,3-d_2 was obtained from the acid via the acid chloride and the amide by the Hofmann degradation.

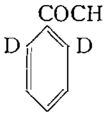
The benzene-1,2-d_2 prepared from the deuterated aniline by deamination analyzed 82.1% $C_6H_4D_2$ and 17.1% C_6H_5D. The slightly low content of deuterium may be due to a small loss of deuterium by exchange in each of the two reactions involving introduction of deuterium. In any event the compound was pure enough isotopically for the purpose. Deamination by means of deuterohypophosphorous acid thus offers a convenient means of replacing an amino group by deuterium in an aromatic compound. Another recent example of its use is the deamination of vicinal xylidine to 1,3-xylene-2-*d* by Fraser (23).

Yet another method of deuterating aromatic compounds is the action of deuterium chloride in the presence of anhydrous aluminum chloride. Klit and Langseth prepared benzene-d_6 by this method (24). The reaction is essentially an exchange catalyzed by the Lewis acid $DAlCl_4$. It probably cannot be used for deuterating in a specific position.

Important confirmation of an earlier prediction by Ingold, Raison, and Wilson (25) was obtained in 1936 when these authors observed a reasonably rapid exchange between benzene and 50 mole % deuterium sulphate in deuterium oxide at room temperature without any appreciable sulphonation. Several years later in continuation of their brilliant work on the spectroscopic investigation of the structure of benzene, Ingold, Wilson, and co-workers turned again to the exchange method to prepare benzene-d_6 and 1,4-dibromobenzene-d_4 (12). In deuterating bromobenzene by this method they were unable to avoid undue sulphonation. Apparently in this case the rates of sulphonation and exchange are very similar. A third deuterobenzene, the 1,3,5-d_3 isomer was prepared from aniline, in which exchange occurs under comparatively milder conditions than in benzene. It is sufficient to heat the hydrochloride in deuterium oxide for a day to establish equilibrium. Deuterium enters the ortho and para positions. After several such exchanges the deuterium in the amino group was washed out with ordinary water and the amine was deaminated to benzene-1,3,5-d_3. Since the paper by Best and Wilson (12) no appreciable use has been made of this reaction to deuterate aromatic compounds.

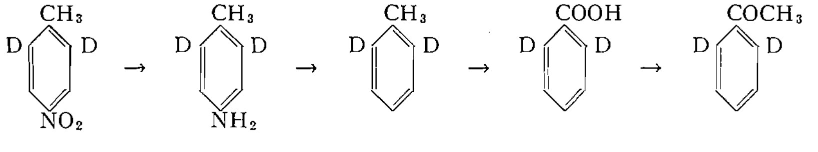
One of the aims of the present work was to extend the exchange method to a variety of substituted benzenes in order to obtain compounds of interest for infrared measurements. Two of these were acetophenone-2-*d* and acetophenone-2,6-d_2. The synthesis of 2-deuteroacetophenone was straightforward. It started with 2-bromotoluene, which was converted to toluene-2-*d* by the Grignard reaction discussed above. The toluene-2-*d* was oxidized to benzoic-2-*d* acid without loss of the deuterium label by alkaline permanganate.





The deuterium was determined by combustion and estimation of the deuterium content of the water by infrared analysis. Acetophenone was prepared from benzoyl-2-*d* chloride and dimethyl cadmium as described by Cason (26).

For the synthesis of acetophenone-2,6-d_2 4-nitrotoluene was found to be a satisfactory starting material.



With 95% deuterium sulphate at 95° C, 4-nitrotoluene underwent exchange in the 2- and 6-positions without much sulphonation. After two exchanges the compound gave no signal in the N.M.R. corresponding to the 2,6-hydrogen atoms. The signal for the 3,5-hydrogen atoms occurs at lower field. The deuteronitrotoluene was reduced with tin and hydrochloric acid; deamination and oxidation took place with complete retention of the deuterium label. The other steps were the same as for the monodeutero compound. It is noteworthy that exchange occurs at the positions predicted by the orienting effects of the methyl and nitro substituents. It is also striking that exchange proceeds so smoothly when it is considered that toluene and nitrobenzene cannot be exchanged without considerable loss due to sulphonation. It has been found that 2- and 3-nitrotoluenes exchange readily with 95% D_2SO_4 to give 2-nitrotoluene-d_4 and 3-nitrotoluene-d_4. In these cases no selective deuteration occurs; all positions are affected by the substituents.

The bromotoluenes were next investigated. 4-Bromotoluene exchanged its ring protons readily in 95% D_2SO_4 at 80° C after 3 hours. Under these conditions 2-bromotoluene was sulphonated even at room temperature. However, 90% D_2SO_4 at room temperature brought about considerable exchange and little sulphonation in 24 hours. After three equilibrations with this acid the ring proton signals in the N.M.R. spectrum were no longer visible. 3-Bromotoluene sulphonated readily in 95% D_2SO_4 at room temperature. Exchanges with 80, 85, and 90% D_2SO_4 at room temperature were carried out without achieving any exchange. No change was apparent in the N.M.R. spectrum of the products.

In connection with a joint project with Lecomte (27) the synthesis of several polychlorodeuterobenzenes by exchange was investigated. 1,4-Dichlorobenzene was readily exchanged in 88 mole % D_2SO_4 as had been reported earlier by Best and Wilson (12) for the dibromo derivative. The more highly chlorinated benzenes such as the 1,3,5-trichloro, the 1,2,4,5-tetrachloro, and the pentachloro were expected to exchange under more drastic conditions due to the deactivating influence of the chlorine atoms. 1,3,5-Trichlorobenzene underwent exchange at 100° C but a temperature of 150° C was required to bring about exchange in the tetra- and penta-chlorobenzenes. Loss due to simultaneous sulphonation was, however, appreciable.

It appears that deuteration of ring protons follows the course to be expected from a consideration of the orienting effects of the substituents. The feasibility of exchange in any given case depends, however, upon the relative rates of sulphonation and exchange.

EXPERIMENTAL

Deamination of p-Nitrobenzenediazonium Fluoborate in Isopropyl Alcohol

p-Nitrobenzenediazonium fluoborate (4.0 g) prepared from *p*-nitroaniline as described by Starkey (28) was added to a suspension of 4.0 g of powdered anhydrous sodium acetate in 10 ml of isopropyl alcohol. Rapid evolution of nitrogen took place and the reaction mixture turned very dark. After the mixture had been standing for an hour the alcohol was removed under vacuum and the residue was taken up in pentane. The pentane solution was then washed with water and dried over a pellet of alkali. The residue which remained after the pentane was distilled off was transferred to a Späth bulb and distilled. Yield of nitrobenzene, 0.5 g (35%).

Deamination of 2-Bromoaniline in Hypophosphorous Acid

2-Bromoaniline (6.88 g, 0.04 mole) was treated, while being stirred, in a 100-ml three-necked round-bottomed flask with 25 ml of 50% hypophosphorous acid. The solution was heated to boiling and then cooled to −5° C. Sodium nitrite (3.0 g) was added in portions to the cold solution. Nitrogen was evolved after each addition of nitrite. The reaction mixture was stirred at 0° C for 3 hours and then poured on ice in a flask equipped for steam distillation. The distillate was taken up in ether, and the solution was dried over a pellet of alkali and then freed of solvent. The residue was purified by distillation on the vacuum line. Yield, 4.8 g (78%); $n_D^{24.5}$, 1.5521.

2-Amino-3-nitrotoluene

This compound was prepared as described in reference 19 in 53% yield.

2-Bromo-3-nitrotoluene

2-Amino-3-nitrotoluene (50 g, 0.3 mole) was dissolved in 160–175 ml of 48% hydrobromic acid heated on a hot plate. The solution was cooled to room temperature while 300 ml of water was slowly added. The solution was diazotized at −12° C with 30 g of sodium nitrite dissolved in 40 ml of water and filtered. The filtrate was added in portions to a solution of cuprous bromide prepared from 60 g of copper sulphate, 24 g of copper turnings, 400 ml of water, and a solution of 60 g of potassium bromide in 270 ml of 48% hydrobromic acid. The mixture was heated for $\frac{1}{2}$ hour on the steam bath and then distilled in steam. Yield, 57 g (81%).

2-Bromo-3-aminotoluene

Activated iron was prepared by mixing 240 g of iron powder and 82 ml of 48% hydrobromic acid as described in reference 20. The mixture was evaporated nearly to dryness in a vacuum evaporator at 60° C. At this stage the mass of activated iron had broken up into small balls which were removed and pulverized in a mortar. Residual moisture was removed on the vacuum line but without further shaking on a water bath at 100° C.

The reduction was carried out using 20 g of 2-bromo-3-aminotoluene as described in the reference cited above except that dioxane was used instead of benzene. The reaction mixture from the reduction was steam-distilled to remove all the dioxane after addition of 80 ml of hydrobromic acid to convert the amine to the hydrobromide. The residue was basified with 35 g of sodium hydroxide in 70 ml of water and steam distillation continued to obtain the amine. The bromotoluidine was taken up in ether in the usual way. The yield of amine recovered from a distillation in a Späth bulb at 60° C under vacuum was 65–70%; n_D^{23}, 1.6034; n_D^{20}, 1.6050.

2-Bromo-3-amino-d_2-toluene

The amine (20.5 g, 0.11 mole) was stirred vigorously at 80° C for 8 hours with 25 ml of deuterium oxide containing one pellet of alkali. The exchanged amine was separated from the water in a separatory funnel and returned to the original flask for a second exchange. Two more exchanges were considered sufficient to replace all the amino hydrogen by deuterium. There was practically no loss during these operations.

Deuterohypophosphorous Acid

Hypophosphorous acid was exchanged 10 times with deuterium oxide as described in reference 22 until the deuterium content as judged from the deuterium content of a sample of benzene-*d*, prepared by deamination of aniline-ND_2, was 95.91%.

2-Bromotoluene-3-d

To 20 g of 2-bromo-3-amino-d_2-toluene in a 250-ml round-bottomed flask with a side arm for a separatory funnel was added, while being cooled in ice water, 58 ml of 50% deuterohypophosphorous acid – deuterium oxide and finally 30 ml of additional deuterium oxide. To the mixture was added, very slowly, a solution of 8.0 g of sodium nitrite in 8 ml of deuterium oxide; during the addition, the temperature was still kept around 0° C, the mixture was stirred, and the rate of nitrogen evolution was observed. The reaction mixture was protected from moisture and kept in the refrigerator overnight. In the morning all the volatile material was distilled on the vacuum line into a Stock trap. The distillate was extracted with ether and the bromotoluene recovered in the vacuum line by distillation. Yield, 10 g (55%). Mass analysis: 93.9% C_7H_6DBr.

In a second run from 17.6 g of amine-d_2 there was obtained 9.4 g of 2-bromotoluene-3-d_1, n_D^{23} 1.5539. The boiling point was 181° C. Yield, 59%. 2-Bromotoluene has n_D^{23} 1.5540, b.p. 181° C. Mass analysis: 95.98% C_7H_6DBr, 4.0% C_7H_7Br.

Toluene-2,3-d_2

Magnesium (0.9 g) was placed in a 100-ml two-necked round-bottomed flask equipped with a separatory funnel and a reflux condenser. The apparatus was connected to a vacuum line flamed and pumped for 1 hour to remove traces of moisture. Dry air (freed of CO_2 by Ascarite) was introduced at the end. A few milliliters of ether dried over sodium wire was added to the magnesium followed by 5.7 g of 2-bromotoluene-3-*d* dissolved in 20 ml of anhydrous ether. Reaction started almost at once. After the solution was stirred for about 3 hours the ether was removed under reduced pressure. The residue was cooled in a bath of ice water and deuterium oxide (7.0 ml) was added dropwise. The toluene that was formed and ether were distilled into a Stock trap. The toluene was taken up in more ether, water was separated, and the ether solution was dried. The ether was removed on the vacuum line keeping the solution at −26° C. It was condensed in a trap cooled in dry ice and acetone at −78° C. During this operation the stopcocks are set so that a little ether distills slowly but continuously from the solution. When the pressure in the system has fallen to 1 mm the residue is virtually free of ether. Yield, 2.3 g (74%). Mass analysis:

	I	II
$C_7H_6D_2$	82.7%	80.1%
C_7H_7D	16.5%	17.8%
C_7H_8	0.6%	1.2%

Benzoic-2,3-d_2 Acid

Toluene-2,3-d_2 (4.5 g, 0.05 mole) and 400 ml of water were heated to boiling under a reflux condenser. Potassium permanganate (15.6 g, 0.1 mole) was added in portions over a period of 4 hours. After being heated under reflux for a further period of 4 hours the reaction mixture was filtered. The filtrate and washings were concentrated under reduced pressure to a volume of 50 ml. The solution was then acidified with concentrated hydrochloric acid (3.2 ml) and the white precipitate of benzoic-2,3-d_2 acid was filtered off and washed once with a little cold water. Yield, 4.3 g (73%); m.p. 123.4° C.

The use of a copper flask as described by Bigelow (29) did not lead to higher yields in test experiments.

Benzoyl-2,3-d_2 Chloride

Benzoic-2,3-d_2 acid (3.8 g, 0.03 mole) was heated under reflux with 4.6 g freshly distilled thionyl chloride for 2 hours. Hydrogen chloride and excess thionyl chloride were pumped off on the vacuum line and the residue was distilled into a Stock trap. Yield, 4.0 g (92%).

Benzamide-2,3-d_2

Benzoyl-2,3-d_2 chloride (4.0 g) was added slowly to 17.0 ml of concentrated ammonium hydroxide while the mixture was being stirred, and cooled in an ice bath. The solid was filtered and washed with cold water. Recrystallization from 17 ml of hot water gave 2.8 g of benzamide-2,3-d_2 (81%), m.p. 127–129° C.

Aniline-2,3-d_2

A solution of 4.2 g of potassium hydroxide in 50 ml of water in a 400-ml beaker was cooled to 0° C in an ice bath. Bromine (4.5 g) was added in one portion and the mixture was stirred until all the bromine had dissolved. Another solution of 6.0 g of potassium hydroxide in 10 ml of water was prepared. Finely powdered benzamide-2,3-d_2 (2.8 g, 0.02 mole) was added all at once to the potassium hypobromite, with vigorous stirring; at the same time there was added the concentrated solution of alkali prepared above. After 5 minutes all the solid had dissolved. The reaction mixture was transferred to a flask set for steam distillation and heated on the steam bath for 2 minutes. The oil which collected on the top was distilled over in a current of steam. The aniline-2,3-d_2 was taken up in ether, dried over alkali, filtered, and freed of solvent. The residue was distilled slowly into a trap in the vacuum line. Yield, 1.8 g (83%); n_D^{20}, 1.5844.

The deuterium content of the aniline was determined by deaminating it to benzene-1,2-d_2. The mass analysis of the latter was 82.1% $C_6H_4D_2$, 17.1% C_6H_5D, and 0.8% C_6H_6.

Deuterium Sulphate

Deuterium sulphate for exchange reactions was prepared by the modification described below of the procedure of Best and Wilson (12).

To a condenser with ground-glass joints set for downward distillation were connected a 1-liter Claisen flask and a receiver with a side arm to which was attached a drying tube filled with glass wool and phosphorus pentoxide. The other end of the drying tube was connected by means of rubber tubing to a filter flask with a controllable leak. No lubricant was used on any of the joints but they were covered with paraffin wax on the outside.

Stabilized sulphur trioxide (300 ml) purchased from Allied Chemical of Canada, Montreal, Quebec, under the name of "Sulfan B" was poured into the distilling flask and 100 g of 99.7% deuterium oxide was weighed into the tared receiver cooled in crushed ice. When the distilling flask was gently heated and slight suction from a glass aspirator pump was applied, sulphur trioxide distilled slowly into the water.

At the end of the distillation an aliquot of deuterium sulphate was removed and analyzed by titration against $N/10$ alkali. The concentration of deuterium sulphate was then adjusted as required by addition of the appropriate amount of deuterium oxide.

4-Nitrotoluene-2,6-d_2

A solution of 7.0 g (0.06 mole) of 4-nitrotoluene in 25 g of 94.81% deuterium sulphate was heated at 90° C for 24 hours. The reaction mixture was cooled, and poured onto cracked ice. The oil was extracted with ether. The ether solution was washed with water, dried over calcium chloride, and freed of solvent. The exchanged 4-nitrotoluene (5.6 g) was equilibrated twice more with fresh quantities of deuterium sulphate.

The course of the exchange was followed by examining the N.M.R. spectrum of the compound. The normal compound shows two doublets spaced 25 c.p.s. apart and 200 c.p.s. lower than the methyl signal. In the exchanged compound the doublet at higher field and therefore corresponding to the 2,6-hydrogen atoms disappeared. The spectrum was essentially unchanged after the third exchange.

4-Nitrobenzoic-2,6-d_2 Acid

4-Nitrotoluene-2,6-d_2 (19.0 g, 0.015 mole) was oxidized with potassium permanganate as described by Bigelow (29) in a Pyrex rather than a copper flask. The yield of 4-nitrobenzoic-2,6-d_2 acid was 17.2 g (78%).

4-Aminobenzoic-2,6-d_2 Acid

The 4-nitro acid was reduced with tin and hydrochloric acid as described by Vogel (30). The yield was 71% of product, m.p. 186–186.5° C.

Benzoic-2,6-d_2 Acid

The amino acid was diazotized and deaminated as described by Kornblum (16). The yield from 10 g of amino acid was 4.9 g (55%), m.p. 121.5–122.0° C. Analysis by combustion gave a deuterium content of 1.96 atoms. All the reactions were therefore carried out without any appreciable loss of deuterium.

Benzoyl-2,6-d_2 Chloride

The chloride was prepared from thionyl chloride as described above for benzoic-2,3-d_2 acid.

Acetophenone-2,6-d_2

The acid chloride was converted into acetophenone exactly as described by Cason (26). The yield was 78% of product, n_D^{25} 1.5296, m.p. 17.5° C. For normal acetophenone, n_D^{25} is 1.5307.

3-Nitrotoluene-d_4

3-Nitrotoluene (6.0 g) was heated with 25 g of 97.3% deuterium sulphate for 24 hours at 75–80° C. The product was worked up as already described for the 4-nitro isomer. Recovery was 91%. Loss due to simultaneous sulphonation is therefore slight. After three exchanges there was no signal observed in the N.M.R. spectrum where the ring hydrogens occur in the light compound.

2-Nitrotoluene-d_4

Nuclear proton exchange was carried out under the same conditions as for the other two isomers. The N.M.R. spectrum indicated that exchange occurred in all positions as expected though more slowly than in the other isomers.

4-Bromotoluene-d_4

A mixture of 7.0 g of 4-bromotoluene (.04 mole) and 25 ml of 95.7% deuterium sulphate was stirred for 24 hours at room temperature. The exchanged 4-bromotoluene was isolated from the reaction mixture as described above. After two more exchanges the ring proton signals in the N.M.R. spectrum had disappeared while the signals due to the protons in the methyl group had their original intensity. All ring protons therefore exchange under these conditions. At 80° C the 4-bromotoluene was almost completely sulphonated after only 3 hours.

Non-exchange of 3-Bromotoluene

In 95.5% deuterium sulphate 3-bromotoluene is almost completely sulphonated after 3 hours at room temperature. Deuterium sulphate diluted with deuterium oxide to 80% acid did not sulphonate 3-bromotoluene at room temperature after 60 hours stirring but there was no change in the N.M.R. spectrum. Evidently no exchange had occurred. At room temperature 85% deuterium sulphate gave about 20% sulphonated product but again there was no evidence of exchange in the recovered 3-bromotoluene. In 90% deuterium sulphate at room temperature the amount of sulphonated product increased but there was still no evidence of exchange as judged from the N.M.R. spectrum. Apparently the rate of sulphonation in 3-bromotoluene is much more rapid than that of exchange.

2-Bromotoluene-d_4

The optimum condition for exchange was to stir 2-bromotoluene at room temperature with 90% deuterium sulphate for 24 hours. More concentrated acid or higher temperature both led to extensive sulphonation. After three exchanges the signal for the ring protons had completely disappeared from the N.M.R. spectrum while the methyl proton signal retained its original intensity.

Non-exchange in 1,2-Dimethyl-4-nitrobenzene

In 97% deuterium sulphate the compound gave only tar. In a second attempt to bring about proton exchange the compound was stirred at room temperature in 85% deuterium sulphate. At this concentration of acid there was 40% loss due to sulphonation but no change in the N.M.R. spectrum of the recovered nitro compound.

2-Chloronitrobenzene-3,5-d_2

2-Chloronitrobenzene (5.5 g) was heated at 70° C in 30 g of 95% deuterium sulphate for 30 hours. The product was isolated in the usual manner. There was hardly any loss due to sulphonation. After a second exchange the N.M.R. spectrum of the compound was measured. Some of the signals for the ring protons were considerably reduced. From a consideration of the orienting effects of the chlorine and nitro groups it would appear that deuteration occurred in the 3- and 5-positions.

p-Dichlorobenzene-d_4

p-Dichlorobenzene (5.0 g) was heated with 45 g of 95% deuterium sulphate at 105° C with stirring for 6 hours. The cold reaction mixture was poured onto cracked ice and the 1,4-dichlorobenzene was filtered off and washed with water. The product obtained after two more exchanges was recrystallized from ethyl alcohol. Yield, 2.5 g (50%); m.p. 54.5° C. The N.M.R. spectrum measured in cyclohexane gave no signal for benzene ring protons.

1,3,5-Trichlorobenzene-d_3

The conditions were essentially those employed to exchange the dichlorobenzene. Two exchanges were sufficient to cause the disappearance of the ring proton signal in the N.M.R. spectrum. The loss due to simultaneous sulphonation was again 50%.

1,2,4,5-Tetrachlorobenzene-d_2

1,2,4,5-Tetrachlorobenzene (5.0 g) and 45 g of 97% deuterium sulphate were heated for 12 hours in a sealed tube at 150° C. The exchanged product was isolated as described for 1,4-dichlorobenzene-d_4 above. After three exchanges 3.2 g of the tetrachloro compound were recovered. It was recrystallized from benzene, m.p. 141.5–142° C. The signal due to the ring protons in the N.M.R. spectrum had completely disappeared.

Pentachlorobenzene

Pentachloronitrobenzene was reduced to pentachloroaniline in dioxane solution with activated iron and water as described above. An excellent yield of pentachloroaniline, m.p. 243–244° C, was obtained.

Pentachloroaniline was deaminated in 50% hypophosphorous acid in the presence of dioxane using isoamyl nitrite as the source of nitrous acid. One gram of the amine was dissolved in 15 ml of dioxane and 15 ml of 50% hypophosphorous acid. The stirred suspension was treated with 2 ml of isoamyl nitrite at room temperature. Nitrogen was slowly evolved for about 2 hours. The reaction mixture was poured into water and the solid filtered off. Recrystallization from ethyl alcohol gave 0.3 g of pentachlorobenzene, m.p. 84° C. The product was also purified by sublimation *in vacuo* from a bath at 70° C.

Pentachlorobenzene-d

The exchange was carried out with 97% deuterium sulphate as described for tetrachlorobenzene. Evidence of exchange having taken place was obtained from both N.M.R. and infrared spectra. The treatment with acid seemed to remove a small amount of impurity as the melting point of the exchanged product was raised to 86.5° C.

The compound was also prepared by deamination of pentachloroaniline in 50% deuterohypophosphorous acid but the pentachlorobenzene-*d* contained some of the normal compound (which probably arose from H in the amino group) and had to be enriched in deuterium by exchange with deuterium sulphate just the same.

ACKNOWLEDGMENTS

The authors wish to thank Mrs. R. H. Riem for several mass analyses, Mrs. M. A. Mackenzie for an analysis by combustion, and Mr. J. R. Nicholson for some N.M.R. spectra.

Thanks are also due to the Olin-Mathieson Chemical Corporation, Baltimore, Maryland, for the gift of a sample of pentachloronitrobenzene.

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