[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, BERKELEY]

Synthetic Routes for Isotopically Labeled 1,5-Hexadiene

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Received July 29, 1960

Synthetic routes were devised which would make possible the preparation of 1,5-hexadiene isotopically labeled in the terminal positions or in the central positions. The reaction sequence which would make possible the synthesis of 1,6-labeled diene was: adipyl chloride → *N,N,N′,N′*-tetramethylamide → 1,6-bisdimethylaminohexane → amine oxide → 1,5-diene. For diene labeled in the central positions this sequence would be preceded by: ethylene dibromide → diethyl adipate → adipyl chloride.

The literature method[2] for the preparation of 1,5-hexadiene of treating allyl chloride with a metal does not lend itself to the synthesis of 1,5-hexadiene isotopically labeled in specific positions. For the synthesis of 1,6-deuterium–labeled diene an adipic acid derivative could be reduced with lithium aluminum deuteride, and the unsaturation introduced by subsequent transformations. A conceivable reaction sequence could be: diethyl adipate → 1,6-hexanediol → 1,6-dibromohexane → 1,6-diquaternary nitrogen base → 1,5-diene. The troublesome step of this sequence would be expected to be the last. No example of pyrolysis of an open-chain, diquaternary nitrogen base which could lead to an isolated diene could be found in the literature. Blomquist and co-workers[3] have prepared successfully bismethylene cyclic compounds by the pyrolysis of bifunctional quaternary nitrogen bases. These pyrolyses led to the desired conjugated diene, and the formation of an isolated diene was impossible. There are examples[4] of the pyrolysis of unsaturated quaternary nitrogen bases where the expected product would be an isolated diene. In some instances it was possible to obtain a rather poor yield of the isolated diene, but the principal product was usually a conjugated diene which was formed by isomerization of the isolated diene.

The above-mentioned reaction sequence was successful in all steps except the last, and this failed miserably. The 1,6-diquaternary nitrogen base did not undergo elimination satisfactorily, and careful fractional distillation of the pyrolysate gave but a 43% yield of hydrocarbon. Of this material only 4% was acceptable as 1,5-hexadiene on the basis of boiling point and refractive index. From physical constants the bulk of the hydrocarbon appeared to be conjugated hexadienes.

Cope and Bumgardner[5] have been able to convert unsaturated tertiary amines to isolated dienes by pyrolysis of the corresponding amine oxides, and there was no isomerization of the double bonds to a conjugated system. The application of this reaction for the preparation of 1,6-deuterium-labeled-1,5-hexadiene would require the sequence: adipyl chloride → *N,N,N′,N′*-tetramethyl amide → 1,6-bisdimethylaminohexane → amine oxide → 1,5-hexadiene. This sequence proved fairly successful. The amide was reduced to the amine with lithium aluminum hydride in 72% yield and the amine was converted through the amine oxide to a 55% yield of 1,5-hexadiene. This diene exhibited no absorption in the 215–300 mμ region, and this indicated the absence of conjugated diene.

To obtain 1,5-hexadiene isotopically labeled in internal positions one could start with 1,2-dibromoethane which was labeled, and convert this to adipic acid. Such a conversion would involve the reaction of the dibromide with malonic ester to obtain 1,1,4,4-tetracarbethoxybutane, which could be taken to adipic acid. The tetraester has been reported in the literature,[6] and the yield has always been given by the remark that it was low. Cason and Allen[7] have reported that by controlling the relative amounts of sodium, malonic ester, and 1,3-dibromopropane, the reaction could be carried out to give mainly the tetracarbethoxy compound or mainly the 1,1-dicarbethoxycyclobutane. Application of their findings to the reaction with 1,2-dibromoethane produced no significant amount of tetracarbethoxy compound. By taking advantage of Perkin's discovery[8] that 1,1-dicarbethoxycyclopropane would undergo the Michael reaction, it was possible to convert 1,2-dibromoethane to diethyl adipate in a reasonable yield. One mole of dibromoethane in an excess of malonic ester was refluxed with two moles of sodium ethoxide. A third mole of sodium ethoxide was added and the reaction mixture again refluxed. The high-boiling residue from the reaction mixture was hydrolyzed, decarboxyl-

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(2) A Turk and H. Chanan, *Org. Syntheses*, **Coll. Vol. III**, 121 (1955).

(3) A. T. Blomquist *et al.*, *J. Am. Chem. Soc.*, **77**, 1806 (1955); *J. Am. Chem. Soc.*, **78**, 6057 (1956); *J. Am. Chem. Soc.*, **79**, 3916 (1957).

(4) J. Weinstock, *J. Org. Chem.*, **21**, 540 (1956) and references cited therein.

(5) A. C. Cope and C. L. Bumgardner, *J. Am. Chem. Soc.*, **79**, 960 (1957).

(6) J. H. Brewster, *J. Am. Chem. Soc.*, **73**, 366 (1951) and references cited therein.

(7) J. Cason and C. F. Allen, *J. Org. Chem.*, **14**, 1036 (1949).

(8) W. H. Perkin, *J. Chem. Soc.*, **65**, 572 (1894).

ated, and esterified to give a 48% yield of diethyl adipate.

It was not possible to convert satisfactorily diethyl adipate to *N,N,N′,N′*-tetramethyladipamide by treatment of the ester with dimethylamine. Also, it was not feasible to convert the crude adipic acid which was obtained by decarboxylation of the butanetetracarboxylic acid to the acid chloride. To convert 1,2-dibromoethane to 1,5-hexadiene the diethyl adipate obtained from the dibromide would have to be hydrolyzed and the acid taken to the acid chloride. The acid chloride could then be carried through the amide and amine oxide to the diene.

EXPERIMENTAL

1,6-Dibromohexane to diene. A mixture of 132.2 g. (2.24 moles) of anhydrous trimethylamine, 45 ml. of absolute methanol and 60.3 g. (0.247 mole) of 1,6-dibromohexane (b.p. 111–112°/8.5 mm.; n_{D}^{25} 1.5044) was carried through the usual Hofmann elimination procedure. Distillation of the pyrolysate from hydroquinone in a nitrogen atmosphere through a spinning-band column gave the following materials: 0.91 g., b.p. 40.4–58.0°, n_{D}^{25} 1.3765–1.3967; 0.36 g., b.p. 58.0–58.3°, n_{D}^{25} 1.4003; 7.36 g., b.p. 58.3–81.6°, n_{D}^{25} 1.4010–1.4539. Total weight of distillate, 8.63 g., 43% yield of diene. The 1,5-hexadiene reported below had b.p. 58.4°, n_{D}^{25} 1.4005. The literature[9] values for the hexadienes are: 1,3-diene, b.p. 73°, n_{D}^{25} 1.435; 2,4-diene, b.p. 80°, n_{D}^{25} 1.447; 1,5-diene, b.p. 59.5°, n_{D}^{25} 1.4010. From the physical constants it was clear that this method of preparation gave a mixture of hexadienes, and that little 1,5-diene of good purity could be isolated.

N,N,N′,N′-Tetramethyladipamide. In a 2 l., three-necked flask fitted with a stirrer, ice-cooled reflux condenser and inlet tube was placed 70.9 g. (0.387 mole) of adipyl chloride (b.p. 103°/4 mm.) and 1 l. of dry ether. The reaction flask was cooled in an ice water bath. In a second flask was placed 76.8 g. (1.70 moles) of anhydrous dimethylamine, and this flask was connected by means of rubber tubing to the inlet tube of the three necked flask. The dimethylamine was allowed to evaporate into the reaction flask during a period of 1.5 hr., and the reaction mixture allowed to stand at room temperature for a day.

The reaction mixture was transferred with 200 ml. of water rinsings to a beaker, and the mixture stirred until the solid dissolved in the water. To this mixture was added with stirring 23 ml. of concd. hydrochloric acid. The ether layer was separated and extracted with two 100-ml. portions of water. The combined aqueous solutions were placed in a continuous chloroform extractor. After a 12-hr. extraction the bulk of the chloroform was removed from the extract on the steam bath. Residual chloroform could be removed from the residue only by evacuating the flask to 4 mm. and immersing it in a bath at 95°. The residual amide was powdered and placed in a vacuum desiccator over phosphorus pentoxide. The product, 77.1 g., 99.5% yield, had m.p. 82.8–84.0°. For the amide Prelog[10] has reported m.p. 85°.

Diethyl adipate was treated with anhydrous dimethylamine under various conditions, and to obtain reaction it was necessary to heat the reactants in a pressure vessel at 150°. The amide obtained in this case was inferior in purity and yield to that obtained from adipyl chloride.

1,6-Bisdimethylaminohexane. The procedure was based on the suggestions of Mićović and Mihailović.[11] In a 2 l., three necked flask fitted with a stirrer, reflux condenser, and dropping funnel was placed 18.1 g. (0.477 mole) of lithium aluminum hydride and 500 ml. of dry ether. This mixture was refluxed for 2 hr. A solution of 73.5 g. (0.376 mole) of *N,N-N′,N′*-tetramethyladipamide in 600 ml. of 1,2-dimethoxyethane (distilled from lithium aluminum hydride) was added to the reaction mixture at such a rate that refluxing was maintained. The reaction mixture was refluxed for 1.5 hr. after the completion of the addition of the diamide. The reaction flask was cooled in an ice water bath, and the excess hydride decomposed by the dropwise addition of 280 ml. of saturated sodium sulfate. The precipitate was collected in a Büchner funnel and washed with ether. The combined filtrate and washings was shaken in a separatory funnel with a solution of 1200 ml. of water and 80 ml. of concd. hydrochloric acid. The aqueous layer was separated and made strongly alkaline with sodium hydroxide. The diamine was water soluble but it could be extracted with one 250-ml. and five 150-ml. portions of ether. The ether extract was dried with sodium hydroxide pellets.

The ether was removed from the solution through a helix-packed column, and the residue distilled through a helix-packed column (packed portion, 20 mm. o.d. × 110 mm.). The diamine, collected in several fractions, weighed 45.5 g. (72% yield) and had b.p. 104°/16 mm., n_{D}^{25} 1.4333–1.4337.

1,5-Hexadiene. (*Cf.* Cope and Bumgardner.[5]) In a flask fitted with a stirrer was placed 42.6 g. (0.247 mole) of 1,6-bisdimethylaminohexane. The flask was cooled in an ice water bath, and 158 ml. (containing 1.482 moles of hydrogen peroxide) of 30% hydrogen peroxide was added dropwise to the diamine. The reaction mixture was homogeneous, and was allowed to stand at room temperature for 2 days. At this point the reaction mixture did not color phenolphthalein. The excess peroxide was destroyed by stirring the reaction mixture with platinum black,[12] first for 10 hr. with cooling and then for 36 hr. at room temperature. The platinum was removed by filtration, and the filtrate concentrated with a rotary evaporator at a pressure of 12 mm. During the evaporation the flask containing the reaction mixture was in a bath which was kept at 35°.

For pyrolysis the flask containing the light yellow-colored sirup was fitted with a helix-packed column and a capillary tube which carried nitrogen. For condensation there was a Dry Ice–cooled trap followed by a liquid nitrogen-cooled trap. The pyrolysis system was evacuated to 56 mm., and the temperature of the oil bath surrounding the pyrolysis flask gradually increased. The material in the flask eventually solidified, and did not pyrolyze at a reasonable rate until the oil bath reached a temperature of 190°. After 2 hr. at 190° the pyrolysis flask was virtually empty. The condensate was warmed, mixed with water, and neutralized with sulfuric acid. The organic layer was separated, washed once with water, and placed over freshly heated sodium sulfate.

The organic layer was distilled from hydroquinone in a nitrogen atmosphere through a spinning-band column. After a small low-boiling fraction there were collected several fractions of combined weight 11.16 g. (55% yield), b.p. 58.2–58.4°/755 mm., n_{D}^{25} 1.4004–1.4007. The literature[9] values for 1,5-hexadiene are b.p. 59.5°/760 mm., n_{D}^{25} 1.4010. The absence of conjugated diene in this product was shown by the absence of absorption at 215–300 mμ.

1,2-Dibromoethane to diethyl adipate. In a 1 l., three necked flask fitted with a stirrer, reflux condenser, and dropping funnel were placed 150 ml. of absolute alcohol[13] and 7.4 g. (0.32 g.-atom) of sodium. After dissolution of the sodium, 153.8 g. (0.96 mole) of diethyl malonate (b.p. 97.4°/16 mm.) was added to the flask. The reaction mixture was refluxed,

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[9] F. D. Rossini *et al.*, *Selected Values of Physical and Thermodynamic Properties of Hydrocarbons and Related Compounds*, Carnegie Press, Pittsburgh, Pa., 1953, p. 63.

[10] V. Prelog, *Collection Czechoslov. Chem. Comm.*, **2**, 712 (1930); *Chem. Abstr.*, **25**, 1218 (1931).

[11] V. M. Mićović and M. L. Mihailović, *J. Org. Chem.*, **18**, 1190 (1953).

[12] R. Feulgen, *Ber.*, **54**, 360 (1921).

[13] R. H. Manske, *J. Am. Chem. Soc.*, **53**, 1104 (1931).

and 30.1 g. (0.16 mole) of 1,2-dibromoethane (b.p. 130°/762 mm.) was added dropwise during 0.76 hr. The reaction mixture was refluxed for an additional hour, and then a solution of 3.7 g. (0.16 g.-atom) of sodium in 100 ml. of absolute alcohol was added. After refluxing the reaction mixture for 4 hr., 185 ml. of alcohol was distilled during 1 hr. from the mixture by warming the reaction flask on the steam bath. The residue was cooled and poured into 600 ml. of ice-cold water. This mixture was extracted with one 300-ml. and four 100-ml. portions of ether. The ether extract was dried over freshly heated sodium sulfate.

After removal of the drying agent, the ether was removed through a helix-packed column. The residue was distilled through an 18 mm. o.d. × 165 mm. helix-packed column. When the oil bath used to heat the distilling flask reached 190°, the distillation was interrupted. Distillate weighing 95.0 g., b.p. 84–86°/9 mm., n_D^{25} 1.4117–1.4185, was collected, and 36.9 g. of residue remained in the flask. Pertinent refractive indexes are: diethyl malonate, n_D^{25} 1.4118; 1,1-dicarbethoxycyclopropane, n_D^{20} 1.4331; 1,1,4,4-tetracarbethoxybutane, n_D^{25} 1.4470.

The residue was stirred and refluxed with 50 ml. of concd. hydrochloric acid and 100 ml. of water for 4 hr. The mixture was filtered, and the filtrate evaporated to dryness *in vacuo* in a rotary evaporator. Water was added to the residue, and the solution again evaporated to dryness. The flask containing the solid residue was immersed in an oil bath at 180–185° until evolution of gas ceased. The residue was refluxed for 24 hr. with 170 ml. of absolute alcohol and 1 ml. of concd. sulfuric acid. This solution was poured into 700 ml. of water, and this mixture placed in a continuous benzene extractor. The benzene extract was dried over sodium sulfate, the benzene removed through a helix-packed column, and the residue distilled through a 12 mm. o.d. ×90 mm. helix-packed column to give several fractions (15.6 g., 48% yield) of diethyl adipate, b.p. 125–126°/9 mm., n_D^{25} 1.4260–1.4268. Authentic diethyl adipate had n_D^{25} 1.4254.

A second experiment was carried out with the same quantities of materials. After the first reflux and before addition of the second quantity of sodium ethoxide the reaction mixture was poured into water, the mixture extracted with ether, and the ether solution distilled. After removal of the ether there was obtained 140.8 g., b.p. 86–96°/9 mm., of distillate and 9.5 g. of high-boiling residue. This 9.5 g. of residue provided that not much tetracarbethoxy compound was formed during the first reflux with sodium ethoxide, and that the reaction proceeded primarily to give cyclic product. The 140.8 g. of distillate was refluxed with a second portion of sodium ethoxide, and the reaction mixture worked up as described above to obtain the high-boiling residue. The combined high-boiling residue was hydrolyzed, decarboxylated, and esterified to give a 49% yield of diethyl adipate, b.p. 126°/9 mm., n_D^{25} 1.4259.

1,2-Dibromoethane to adipyl chloride. The reaction was carried out as described above to obtain diethyl adipate. After the high-boiling residue was hydrolyzed and decarboxylated, the residue was refluxed with thionyl chloride. Much solid was formed and only a 25% yield (based on dibromide) of adipyl chloride was obtainable. It was clear that the preferred way to get the adipic acid from the reaction mixture was by esterification.

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The Preparation and Reaction of Some Substituted Benzotrifluorides

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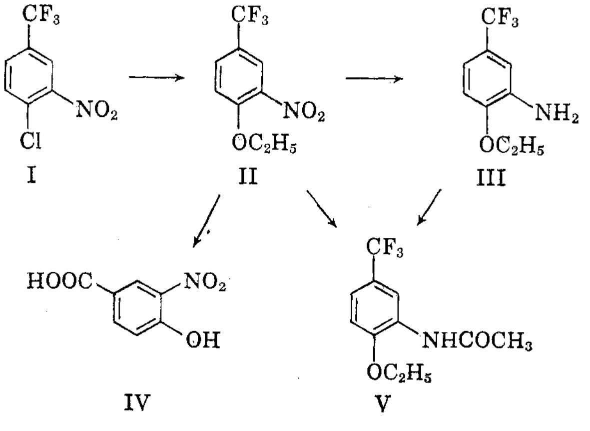
Received August 22, 1960

The preparation of several substituted benzotrifluorides is described, and a few reactions of these benzotrifluorides are noted.

In connection with some other work in these laboratories it became of interest to study the properties and synthesis of several amino and acetamido derivatives of benzotrifluoride having an ether function. Accordingly the synthesis of the isomers 3-amino-4-ethoxybenzotrifluoride (III) and 5-amino-4-ethoxybenzotrifluoride and their corresponding acetyl derivatives was undertaken.



4-Chloro-3-nitrobenzotrifluoride (I) was treated with ethanolic potassium hydroxide to give 4-ethoxy-3-nitrobenzotrifluoride (II), which was converted to III by reduction. The corresponding acetyl derivative V was formed directly from III and by reductive acetylation from II. A similar sequence starting from 2-chloro-5-nitrobenzotrifluoride yielded 5-amino-3-ethoxybenzotrifluoride and its acetyl derivative, 5-acetamido-2-ethoxybenzotrifluoride. The structure of the intermediate nitro compounds II and 2-ethoxy-5-nitrobenzotrifluoride was demonstrated by hydrolysis to the

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