Preparation of Carbon Isotopically Labelled Thiophenes

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As a pre-requisite for a complete determination of the structure of thiophene by microwave technique, enriched samples of 2-^{13}C- and 3-^{13}C-thiophene have been prepared. The methods given below were adopted after repeated experiments with non-labelled compounds. The purity of the resulting isotopically labelled samples was satisfactorily checked by controlling the vapor-pressure and by recording the infra-red absorption curves. Microwave lines from the ^{13}C-labelled species appeared with expected intensity. No lines from impurities were observed in the microwave region, but the infra-red spectra showed the presence of about 5 % CS_2.

Experimental. Preparation of 2-^{13}C-thiophene. Ethylene bromide (3.99 g, 0.0212 mole) and 2.90 g (0.0446 mole) of potassium cyanide, 22 % enriched in ^{13}C, were placed in a 50 ml glass ampulla with 5.2 ml of water and 10.5 ml ethanol. The ampulla was sealed-off under a high vacuum and heated for 3 h on a steam bath under occasional shaking, after which the contents were transferred to a small distilling flask. 10 ml of water and 20 ml of conc. hydrochloric acid was added. Water, ethanol and surplus halogen acids were removed by a slow distillation (1—2 h) at atmospheric pressure, the final temperature of the oilbath applied being 180°C. During this distillation the hydrolysis of the dicyanide is completed. The remainder was quantitatively transferred to a 1 l beaker by means of 200 ml water. 24 g crystalline $BaCl_2$ was added and dissolved. Also, 400 ml of ethanol were added. At this stage, minor quantities of solid impurities were filtered off. 6 ml conc. NH_4OH was added to the filtrate, hereby causing barium succinate (I) to precipitate. The yield was 4.46 g (0.0175 mole). Its purity was checked by comparing its infra-red spectrum (1 mg sample to 300 mg KBr, disk technique) with the spectrum of an authentic sample.

4.46 g (I) was transformed to sodium succinate (II) by adding 50 ml of water and 5.58 g of Na_2SO_4,10 H_2O (0.0174 mole). This mixture was shaken vigorously for 18 h, followed by removal of the $BaSO_4$-precipitate by filtering, whereafter the filtrate was evaporated to dryness. 2.84 g of (II) was obtained, its purity being checked as above. A completely dry sample is essential for the final transformation into thiophene.

2.84 g of (II) was thoroughly mixed with 13 g P_4S_6 (from P and S) [1] in a 50 ml reaction flask which could be heated and swept with dry N_2. The flask was immersed in a bath of 110°C and quickly heated to 300°C. At this temperature a gas mixture was evolved, carried off by the stream of N_2, and finally condensed in a liquid-air cooled trap. After 30 min. heating at 300—310°C the trapped, volatile products (*e.g.* H_2S) were removed by distillation *in vacuo*, the liquid-air bath being substituted by a dry-ice bath. The remainder was distilled *in vacuo* at room temperature into a fresh ampulla containing crushed NaOH pellets in order to retain mercaptanes, CS_2, *etc.* After one hour the liquid product was distilled *in vacuo* onto fresh NaOH, this time allowing for a contact period of 24 h. After a new distillation *in vacuo* the final product had the correct vapor-pressure (21.5 ± 0.5 mm at 0°C). The infra-red spectrum indicated about 95 % purity, a 5 % impurity apparently consisting entirely of CS_2. Since microwaves are not absorbed by CS_2 the purity was satisfactory for our purpose. The contents of 2,5-^{13}C-thiophene (4 %) did not interfere with the spectral interpretation. The yield of 2-^{13}C-thiophene (30 % enriched) was 430 mg (0.0051 mole), representing 23 % with respect to applied, enriched potassium cyanide.

As to the reproducibility of the procedure, compare the next section.

Preparation of 3-^{13}C-thiophene. 1.63 g (0.025 mole) K^{13}CN (22 % enriched in ^{13}C) was transformed into 0.93 g enriched $CH_3{}^{13}CH_2OH$ (0.020 mole), following our earlier procedure [2]. This quantity of ethanol was mixed with 25 g P_2O_5 in a 350 ml glas ampulla, evacuated and sealed-off. After 1.5 h heating at 180°—190°C the volatile products were condensed. By distillation *in vacuo* from a dry-ice bath, 0.0175 mole of gaseous ethylene of high purity (~ 98 %) was collected. In a new ampulla, 0.0166 mole of bromine was reacted with all the ethylene at room temperature, admitting small quantities of ethylene at a time. 0.0166 mole of ethylene bromide was formed, the

purity of which was assumed equal to the purity of ethylene bromide, produced in model experiments and checked by its infra-red spectrum. From hereon the procedure given under 2-^{13}C-thiophene was followed. The final yield of 3-^{13}C-thiophene was 0.0061 mole (510 mg), 22 % enriched in ^{13}C and with no carbon isotopic impurities other than thiophene. The over-all yield thus becomes 24 % as compared to 23 % in the previous case.

These syntheses are of value not only to spectroscopists wanting the ^{13}C-species but also to biochemists wanting radioactive labelled ^{14}C-thiophene or one of its derivatives.

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