

## Synthesis of Alpha- and Beta Carbon Isotopically Labeled Furan

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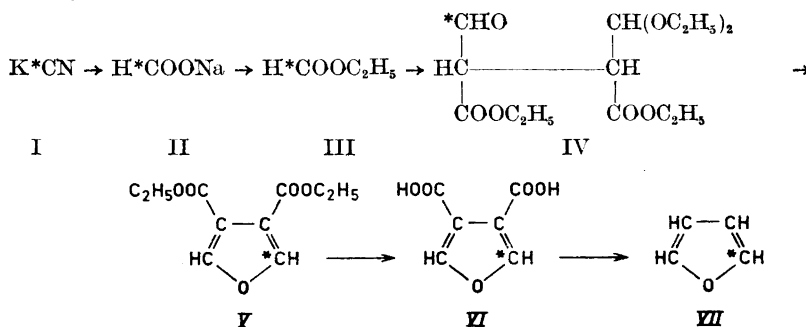
The preparation of 200 mg quantities of 22 % enriched [ $\alpha$ - $^{13}\text{C}$ ]furan and [ $\beta$ - $^{13}\text{C}$ ]furan from enriched  $\text{K}^{13}\text{CN}$  is described. The over-all yields are, respectively, 11 and 8 % with respect to  $\text{K}^{13}\text{CN}$ . The first synthesis involves 6 steps, the second 17 steps. The purity, as controlled by the infrared gas-spectrum, was highly satisfactory.

To the best of our knowledge, enriched [ $\alpha$ - $^{13}\text{C}$ ]— and [ $\beta$ - $^{13}\text{C}$ ]furan have never been synthesized. Their preparation is of interest to the spectroscopist who wants to find the structure of furan by means of the so-called substitution procedure, in which changes in rotational constants, caused by substitution of one atom ( $^{12}\text{C}$ ) by ( $^{13}\text{C}$ ), serve as basis for a calculation of the position of the atom in question.

Also, our procedures worked out may probably serve well in the case of  $^{14}\text{C}$ -synthetic work with furan, thus enabling the biologist to follow the role of furan or furan derivatives in the metabolism of living organisms.

### [ $\alpha$ - $^{13}\text{C}$ ]FURAN

The sequence of reactions was as follows\*:



\* The asterisk indicates the position which is enriched by  $^{13}\text{C}$ .

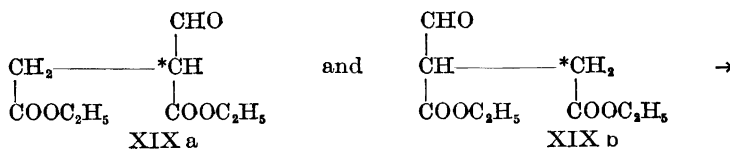
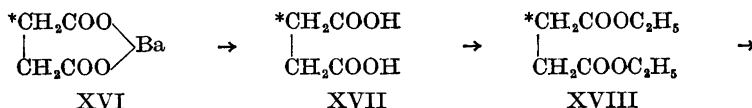
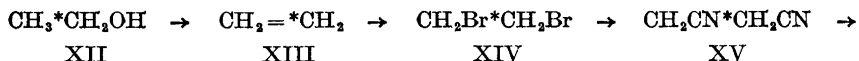
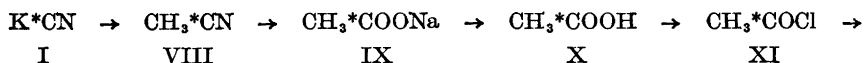
Essentially following Grant and Turner<sup>1</sup>, we converted 6.05 g (0.0929 mole) of commercial, 22 % enriched  $K^{13}CN$  (I) to 5.58 g (0.0820 mole) of  $H^{13}COONa$  (II). Conversion of this salt to ethyl  $[^{13}C]$ formate (III) was carried out according to Burr's procedure<sup>2</sup>. The yield, 6.36 g (0.0857 mole), showed the presence of an impurity, unimportant for the following steps. Formylation<sup>3</sup> of 11.55 g (0.0418 mole) diethyl  $\alpha$ -diethoxymethylsuccinate by means of 6.21 g (III) resulted in 6.66 g (0.0219 mole) of diethyl  $\alpha$ - $[^{13}C]$ formyl- $\beta$ -diethoxymethylsuccinate (IV). The infrared spectrum of (IV) showed it to be pure as compared with the spectrum of 'ordinary', highly purified (IV). Conversion<sup>3</sup> of 6.54 g (0.0215 mole) (IV) to diethyl  $[\alpha\text{-}^{13}C]$ furan- $\beta,\beta'$ -dicarboxylate (V) resulted in 3.65 g (0.0172 mole) of (V), the infrared spectrum of which was satisfactory.

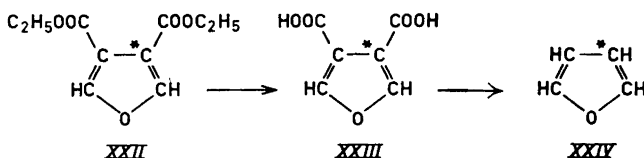
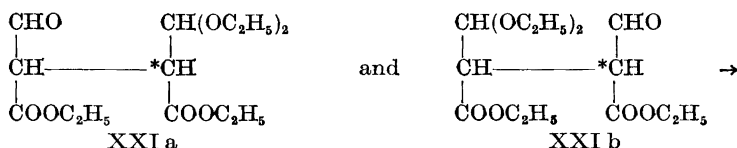
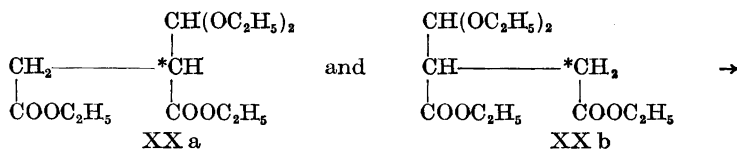
3.52 g (0.0166 mole) of (V) was converted to  $[\alpha\text{-}^{13}C]$ furan- $\beta,\beta'$ -dicarboxylic acid (VI) by refluxing with 25 ml 2.5 N NaOH for 2½ h, cooling, filtering, addition of 4 ml of water, and subsequent removal of 3 ml solvent by distillation. Addition of 10 ml conc. HCl caused (VI) to precipitate. Filtering and drying for 24 h *in vacuo* over  $P_2O_5$  and NaOH resulted in a yield of 2.20 g (0.0141 mole) of (VI), the infrared spectrum of which was satisfactory.

Only part of (VI) was converted into  $[\alpha\text{-}^{13}C]$ furan (VII). 750 mg of (VI) mixed with 400 mg Cu, 400 mg CuO, and 5 ml quinoline was heated for 2 h at 180°–190°C in an evacuated, sealed off ampulla. Hereafter, the  $CO_2$  produced was removed by distillation *in vacuo* at –80°C. (VII) was collected by subsequent distillation at 0°C *in vacuo*. After 1 h exposure to finely divided NaOH and subsequent distillation, 235 mg (0.0035 mole) of pure (VII) was obtained, its infrared absorption curve being satisfactory. Based on the initial 0.0929 moles of enriched  $K^{13}CN$ , the over-all yield of this 6-step synthesis was 11 %.

### $[\beta\text{-}^{13}C]$ FURAN

The sequence of reactions was as follows:





Methyl iodide was converted to  $\text{CH}_3^{13}\text{COONa}$  (IX) following Cox *et al.*<sup>4</sup> 1.96 g (0.0301 mole) of commercial 22 % enriched  $\text{K}^{13}\text{CN}$  was used, resulting in 2.24 g (0.0273 mole) of (IX). The procedure, being unsuited for use in larger scale, was repeated 3 times so that eventually 8.79 g (0.1071 mole) of (IX) was obtained. Following Cox and Turner<sup>5</sup>, (IX) was converted to 6.15 g (0.1022 mole) of  $\text{CH}_3^{13}\text{COOH}$  (X). (X) was transformed into 7.78 g (0.0990 mole) of  $\text{CH}_3^{13}\text{COCl}$  (XI). In two separate operations, 4.02 g, respectively 3.76 g of (XI) were reduced to a combined quantity, 4.26 g (0.0923 mole) of  $\text{CH}_3^{13}\text{CH}_2\text{OH}$  (XII), which in its turn<sup>6</sup>, was converted into 14.58 g (0.0775 mole) of (XIV).

This quantity of (XIV) was converted into  $[\alpha\text{-}^{13}\text{C}]$ succinonitrile (XV)<sup>6</sup> and barium  $[\alpha\text{-}^{13}\text{C}]$ succinate (XVI)<sup>6</sup>, 16.60 g (0.0655 mole), which was transformed into  $[\alpha\text{-}^{13}\text{C}]$ succinic acid (XVII) by means of 6.50 g (0.0649 mole) conc.  $\text{H}_2\text{SO}_4$ , dissolved in 200 ml of water, stirring the mixture over-night. After filtering and removal of water (XVII) esterification was performed<sup>7</sup>, resulting in 10.30 g (0.0592 mole) diethyl  $[\alpha\text{-}^{13}\text{C}]$ succinate (XVIII).

Formylation of 10.10 g (XVIII) with ethyl formate<sup>3</sup> gave 8.45 g (0.0418 mole) of a mixture of diethyl  $\alpha$ -formyl- $[\alpha\text{-}^{13}\text{C}]$ succinate (XIX a) and diethyl  $\beta$ -formyl- $[\alpha\text{-}^{13}\text{C}]$ succinate (XIX b), 8.34 g of which was converted to 10.16 g (0.0368 mole) of diethyl  $\alpha$ -diethoxymethyl- $[\alpha\text{-}^{13}\text{C}]$ succinate (XX a) and diethyl  $\beta$ -diethoxymethyl- $[\alpha\text{-}^{13}\text{C}]$ succinate (XX b). Repeated formylation<sup>3</sup> with ethyl formate of 10.06 g of (XX a) and (XX b) gave 6.06 g (0.0199 mole) of diethyl  $\alpha$ -diethoxymethyl- $\beta$ -formyl- $[\alpha\text{-}^{13}\text{C}]$ succinate (XXI a) and diethyl- $\beta$ -diethoxymethyl- $\alpha$ -formyl- $[\alpha\text{-}^{13}\text{C}]$ succinate (XXI b).

Ring closure<sup>3</sup> resulted in 3.36 g (0.0158 mole) of diethyl  $[\beta\text{-}^{13}\text{C}]$ furan- $\beta,\beta'$ -dicarboxylate (XXII) from 5.94 g (XXI a) and (XXI b).

Infrared control of the products  $\text{XVI} \rightarrow \text{XXII}$  was satisfactory.

Transformation of 3.32 g (0.0157 mole) of (XXII) to 2.15 g (0.0138 mole) of [ $\beta$ - $^{13}\text{C}$ ]furan- $\beta,\beta'$ -dicarboxylic acid (XXIII) and subsequent conversion of part of (XXIII), 750 mg, to 230 mg (0.0034 mole) of [ $\beta$ - $^{13}\text{C}$ ]furan (XXIV) were carried out as indicated under [ $\alpha$ - $^{13}\text{C}$ ]furan.

Based on the initial 0.1204 moles of enriched  $\text{K}^{13}\text{CN}$ , the over-all yield of this 17-step synthesis was 8 %.

## REFERENCES

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