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[^{14}C]-BONAFTON

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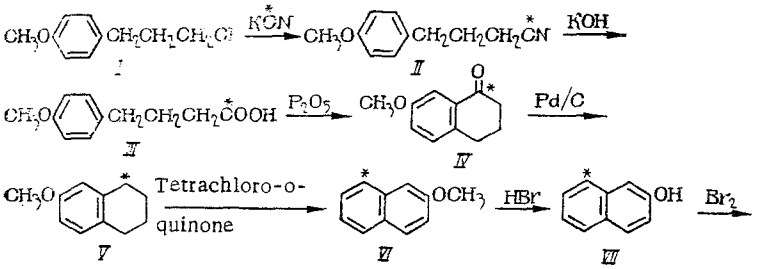
Bonafton [1], a substance with an antiviral action, is 6-bromo-1,2-naphthoquinone. It can be synthesized by oxidizing 6-bromo-2-naphthol with Frémy's salt [2].

The introduction of ^{14}C in the naphthalene ring involves certain difficulties. It was assumed that it would be possible to effect the ring closure of m-bromobenzylidenepyruvic acid (which can readily be obtained from m-bromobenzaldehyde and [^{14}C]-pyruvic acid) to bonafton directly by analogy with a reaction described in the literature [3]. However, in the present case, 6-bromo-1,2-naphthoquinone is not formed either under conditions recommended for the production of analogous compounds [3] or with the aid of other known water-abstracting agents. To synthesize 2-naphthol, we employed in part a method proposed previously [4], making fundamental changes in it. The greatest difficulties in the development of a model synthesis were encountered at the stage of the aromatization of methoxytetralin to methoxynaphthalene (see the scheme of the synthesis). Methoxytetralin does not undergo dehydrogenation with the reagents usually used† (sulfur [5], palladium [6], tetrachloro-p-quinone [7]), while under similar conditions tetralin gave naphthalene in satisfactory yields. It was found possible to perform the aromatization of methoxytetralin with the aid of tetrachloro-o-quinone. We performed the oxidation to bonafton with Frémy's salt [2], since this method is convenient in working with small amounts, although the labelled product obtained proved to have a low radiochemical purity (see Experimental) and required additional chromatographic purification on a silica gel column.



†The reactions were monitored by gas–liquid chromatography.

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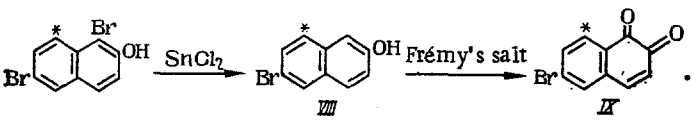

EXPERIMENTAL

[^{14}C]-p-Methoxyphenylbutyronitrile (II). With stirring at 125°C, 1 g of potassium [^{14}C]-cyanide with a total activity of 50 mCi was dissolved in 15 ml of dry dimethyl sulfoxide. Heating was stopped, and 3 g of 1-chloro-3-(p-methoxyphenyl)propane (I) was added at such a rate that the temperature did not rise above 135°C. After the addition of the whole amount of (I), the mixture was stirred at 135°C for 20 min and then at 155°C for another 15 min. After this, it was cooled to 0°C, the mineral salts were filtered off, and the filtrate was poured into 50 ml of ice water. The nitrile (II) was extracted with ether, and the ether was evaporated off. The residue consisted of a yellow, oily liquid.

[^{14}C]-p-Methoxyphenylbutyric Acid (III). The nitrile (II) was treated with a solution of 2 g of caustic potash in a mixture of 5 ml of water and 5 ml of ethylene glycol. The mixture was boiled under reflux for 4 h. Then it was cooled to 10-15°C, 15 ml of water was added, and the organic impurities were extracted with ether. The aqueous solution was cooled to 5°C and the (III) was isolated by acidification with concentrated hydrochloric acid. After drying, 2.56 g of (III) with a total activity of 43.0 mCi and a specific activity of 16.8 mCi/g, was obtained. The radiochemical yield in the two stages amounted to 86%.

[^{14}C]-7-Methoxy-1-tetralone (IV). In a flask fitted with a stopper containing a calcium chloride tube, 30 g of polyphosphoric acid was heated to 90°C, and 2.55 g of (III) was added. The mixture was stirred in the boiling water bath for 15 min. Then it was cooled to 5°C and 100 ml of ice water containing pieces of ice was poured in. The mixture was stirred and more ice was added so that the temperature did not rise. The polyphosphoric acid dissolved in the water, and the tetralone (IV) precipitated. It was filtered off and washed with water to neutrality. After drying, 2.15 g of (IV) was obtained in the form of a cream-colored powder. The total activity was 37.8 mCi, and the specific activity 18.05 mCi/g. The radiochemical yield was 90%.

[^{14}C]-7-Methoxytetralin (V). Compound (IV) was hydrogenated over a 10% Pd/C catalyst in ethanol in the usual way, using 0.2 g of catalyst per 2.15 g of (IV). The process was continued until the absorption of hydrogen ceased. Usually, 20-25% more than the theoretical amount was absorbed. After the ethanol had been distilled off, compound (V) was obtained in the form of a yellow, oily liquid

[^{14}C]-2-Methoxynaphthalene ([^{14}C]-nerolin) (VI). The (V) from the preceding experiment was treated with 30 ml of benzene and 3 g of tetrachloro-o-quinone. The mixture was boiled for 3 h. The benzene was distilled off to dryness, 50 ml of water was added, and the (VI) was steam distilled. Distillation was continued until the condensate had become completely transparent. The (VI) was filtered off and dried over phosphorus pentoxide. This gave 0.903 g of substance with a total activity of 17.75 mCi and a specific activity of 19.75 mCi/g. The radiochemical yield in the two stages was 47%.

[^{14}C]-2-Naphthol (VII). To 0.89 g of (VI) was added a mixture of 2.5 ml of 40% hydrobromic acid and 1.8 ml of acetic anhydride. The mixture was boiled until the oil on the surface of the liquid had disappeared completely (3 h). Then the solution was cooled and 15 ml of ice water was added, whereupon the (VII) separated out in the form of a fine pink precipitate. It was filtered off, washed with water to neutrality, and dried over phosphorus pentoxide, giving 0.73 g of product. The chemical yield was 90%. The specific activity was not determined.

[^{14}C]-6-Bromo-2-naphthol (VIII). A solution of 0.73 g of (VII) in 2.5 ml of glacial acetic acid was treated dropwise with 0.53 ml of bromine in 0.6 ml of glacial acetic acid. After the end of the addition, a precipitate deposited. Then 0.6 ml of water was added and the mixture was heated to the boil. Another 1.5 ml of glacial acetic acid was added to the hot solution and the mixture was heated to 130°C (bath temperature). The solid matter dissolved. Then 2.3 g of stannous chloride was carefully added, and this was followed by 5 ml of concentrated hydrochloric acid. With stirring, the bath temperature was gradually reduced to 80°C and the solution was poured into 15 ml of water. The light pink precipitate was filtered off, washed with water, and dried over calcium chloride, giving 0.9 g of (VIII). The chemical yield calculated on the (VII) was 79.5%. The specific activity was not determined.

[^{14}C]-Bonafton (IX). The compound (VIII) (0.9 g) was dissolved in 90 ml of acetone, 16 ml of 2 N acetic acid was added and then, with stirring, a solution of 1.27 g of monopotassium phosphate in 200 ml of water. After this, 2.7 g of Frémy's salt was added in one portion. The color of the solution gradually changed from violet to red-brown and a precipitate deposited. After 1 h, the precipitate was filtered off and washed with water. After drying, 0.784 g of (IX) was obtained in the form of a light brown powder. The chemical yield of the technical product was 82%.

Purification of the [^{14}C]-Bonafton. The radiochemical purity of (IX) according to the counting of a chromatogram on Silufol in the chloroform–formic acid system was 65%; the technical (IX) contained 35% of radiochemical impurities.

The technical (IX) was subjected to chromatographic purification in a column of silica gel. It was eluted with a mixture of chloroform and 98% formic acid (98:2). The process was monitored by thin-layer chromatography in the same system. The combined eluates were evaporated to one tenth volume, and light petroleum ether was added. The orange powder of (IX) was filtered off and was washed on the filter with light petroleum ether.

After drying, 0.47 g of (IX) with a radiochemical purity of 94% was obtained. Its specific activity was 11 mCi/g and its total activity 5.17 mCi. The overall radiochemical yield calculated on the calcium [^{14}C]-cyanide was 10.3%.

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