DRUG SYNTHESIS METHODS AND MANUFACTURING TECHNOLOGY

11H-DIBENZO[b,e]AZEPINES. PART 2. SYNTHESIS OF 10-^{15}N-DIBENZO[b,f][1,4]OXAZEPINE

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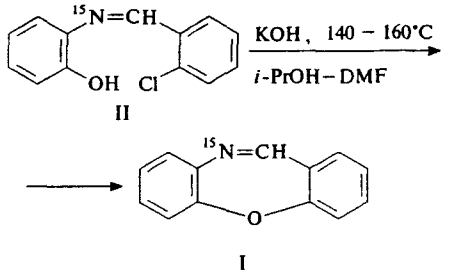
Harrison et al. [1, 2] described the synthesis of dibenzo[b,e]azepines containing carbon and hydrogen isotopes in the azomethine group.

In continuation of the previous work [3] aimed at studying the metabolism of physiologically active dibenzo[b,e]azepines, we have developed a method for the synthesis of compounds containing ^{15}N isotope in the azomethine group. Below we describe this method applied to the synthesis of 10-^{15}N-dibenzo[b,f][1,4]oxazepine (I).

Labeled compound I is obtained in satisfactory yield by boiling a solution of potassium salt of ^{15}N-2-chlorobenzylidene-2′-hydroxyaniline (II) in DMF:



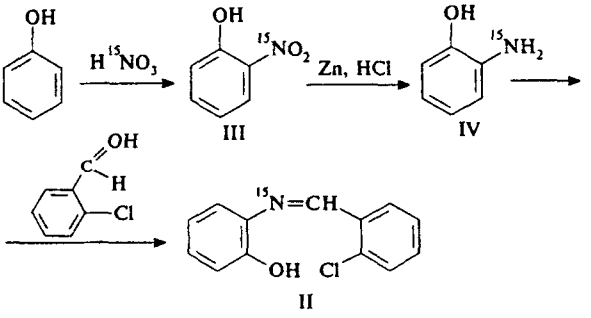
II I

The course of the reaction was monitored by TLC.

The IR spectrum contains absorption bands at 3076 and 3026 cm^{-1} (corresponding to the C–H stretching vibrations of benzene rings), 1603, 1388, and 899 cm^{-1} (^{15}N=C and ^{15}N–C stretching and ^{15}N=CH bending vibrations), and 1277 cm^{-1} (C–O–C), which confirms the proposed structure [3].

Neither boiling of compound II in chloroform, acetonitrile, or *n*-dichlorobenzene, nor its heating to 160 – 180°C in the absence of solvents resulted in the formation of compound I.

Intermediate ^{15}N-containing compounds involved in the synthesis of I were obtained by the following scheme:



II

EXPERIMENTAL PART

The IR absorption spectra were measured on a Perkin-Elmer Model 580B spectrophotometer using CCl_4 as the solvent. The purity of the synthesized compounds was checked by TLC on Silufol UV-254 plates eluted in a benzene – hexane – ethyl acetate (1 : 1 : 1) system.

^{15}N-2-Nitrophenol (III) was obtained by nitriding phenol with ^{15}N-nitric acid (d_4^{20} = 1.28 g/cm^3) at 60 – 70°C in an ethyl acetate solution in the presence of sulfuric acid (d_4^{20} = 1.86 g/cm^3). Yield of compound III, 35 – 45%; m.p., 45.5°C. According to TLC data, no ^{15}N-4-nitrophenol is formed under these reaction conditions.

^{15}N-2-Aminophenol (IV) was obtained by reducing compound III as described in [4]; yield of compound IV, 75%; m.p., 175.5°C.

10-^{15}N-dibenzo[b,f][1,4]oxazepine (I). To compound II obtained from 1.1 g (0.01 mole) of IV and 1.4 g (0.01 mole) of 2-chlorobenzaldehyde was added with stirring 0.5 g

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(0.01 mole) of potassium hydroxide in 20 ml of isopropyl alcohol and 25 ml DMF. After boiling the mixture for 1.5 h, the solvent was distilled off. To the dry residue was added 25 ml of DMF and the mixture was heated for 3 h at 140 – 160°C. Then major part of DMF was evaporated in vacuum and the residue was distilled with water vapor to obtain 1.0 g (59%) of compound I; m.p., 72°C (from 40% aqueous ethanol). Found (%): C, 79.61; H, 4.56; N, 7.08; for $C_{13}H_9N$ anal. calcd. (%): C, 79.98; H, 4.65; N, 7.15.

REFERENCES

1. J. M. Harrison, K. Brewster, and T. D. Inch, *J. Labelled Compd. Radiopharm.*, **14**(3), 369 – 373 (1978).
2. J. M. Harrison, T. D. Inch, and D. A. Upshal, *J. Labelled Compd. Radiopharm.*, **14**(3), 375 – 380 (1978).
3. V. G. Noskov, L. N. Kalinina, M. N. Noskova, et al., *Khim.-Farm. Zh.*, **31**(8), 41 – 43 (1997).
4. H. D. Hartough, S. L. Meisel, and E. Koft, *J. Am. Chem. Soc.*, **70**(12), 4013 – 4017 (1948).