TEBROFEN AND RIODOKSOL LABELLED WITH ^{14}C

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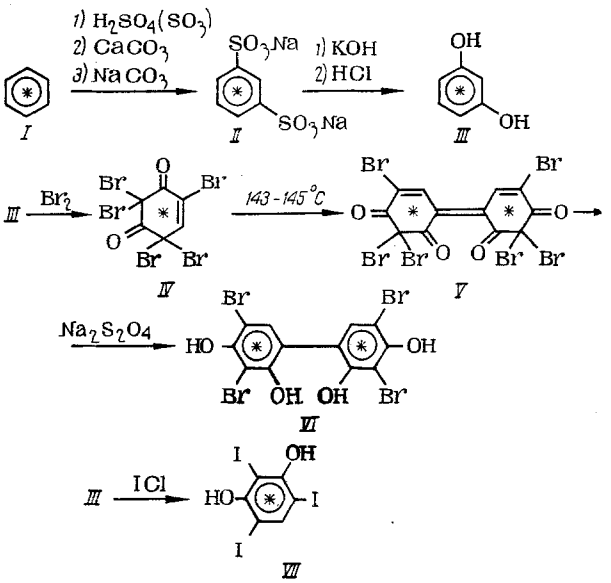
UDC 615.281.8.015.2:615.849.2

In the course of pharmaceutical studies we synthesized the antivirus preparations tebrofen (3,5,3',5'-tetrabromo-2,4,2',4'-tetrahydroxydiphenyl) and riodoksol (2,4,6-triiodoresorcinol) radioactively labelled with ^{14}C. The starting material for the synthesis was [^{14}C]-resorcinol which in turn was prepared from [^{14}C]benzene.



Sulfonation of I afforded the sodium salt of [^{14}C]benzene-m-disulfonic acid (II) by the standard procedure [4], in 83% yield. Caustic fusion of II yielded [^{14}C]resorcinol (III) [5]. Bromination of III yielded pentabromo[^{14}C]resorcinol (IV) [6], which without isolation was thermally decomposed in a bromobenzene medium [1, 7] to bis(3,5,5-tribromo-4,6-dioxocyclohex-2-enylidene) (V). On further reduction with sodium hydrosulfite, we obtained [^{14}C]tebrofen (VI), at a radiochemical yield of 10.3%, calculated from I. Iodination of III with iodine monochloride afforded 2,4,6-triiodo[^{14}C]resorcinol (riodoksol) (VII) [2] at a radiochemical yield of 20.8%, calculated from III.

EXPERIMENTAL

Sodium Salt of [^{14}C]Benzene-m-disulfonic Acid (II). To 1 ml of benzene, with a total activity of 75 mCi, was added 1.5 ml of 20% oleum. The mixture was stirred at 45°C for 1 h. The temperature was then increased to 75°C, and 1.2 ml of 66% oleum was added dropwise, while the temperature was kept below 80°C. The mixture was then heated for 1 h at 90°C, cooled to 25°C, and poured into 25 ml of water.

The [^{14}C]benzene-m-disulfonic acid was converted into the soluble calcium salt, which was separated by filtration from calcium sulfate and treated with sodium carbonate to yield 2.566 g (83%) of II.

[^{14}C]Resorcinol (III). Alkaline fusion was conducted in nickel-plated copper beakers under an argon atmosphere. The beaker was charged with 2.566 g of II and 10.5 g of potassium hydroxide (molar ratio 1:20) and set in Wood's metal. The bath temperature was slowly raised to 310°C where it was held for 1.5 h. The caustic melt was carefully poured into 40 ml of water and neutralized with concentrated hydrochloric acid to pH 4.0. Compound III was

Leningrad Institute of Pharmaceutical Chemistry. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 11, No. 12, pp. 30-32, December, 1977. Original article submitted April 22, 1977.

 0091-150X/77/1112-1612$07.50

extracted with ether (2 × 50 ml). The ether extract was washed with water and dried with anhydrous sodium sulfate. Distilling off the ether under vacuum afforded 0.81 g (79%) of III, mp 109-110°C. The III thus obtained was used without further purification for the synthesis of VI and VII.

Bis(3,5,5-tribromo-4,6-dioxocyclohex-2-enylidene) (V). To a mixture of 2 ml of bromine in 13 ml of water, cooled to 2°C, a solution of 0.81 g of III in 3 ml of water was added dropwise. The reaction temperature was kept below 10°C. When the addition of III was complete the mixture was allowed to stand for 20 min, after which 12 ml of freshly distilled bromobenzene was added. The mixture was stirred for 30 min at 15°C. The organic layer was removed, washed with water (2 × 10 ml), treated with charcoal, and filtered.

The solution of IV in bromobenzene was heated with stirring to 143-145°C and held at that temperature for 30 min, after which the solvent was distilled off under vacuum (20 mm Hg). When the residual liquid began to solidify, the distillation was discontinued and 10 ml of methylene chloride was added. The suspension was cooled to −5°C and kept in the refrigerator for 2 h. The orange crystals were filtered off, washed with 2 ml of cold methylene chloride, and dried, yielding 0.439 g of V, mp 196-199°C. The chemical yield, calculated from III, was 17.2%.

[^{14}C]Tebrofen (VI). To a suspension of 0.439 g of V in 4 ml of 45% isopropyl alcohol, 0.415 g of sodium hydrosulfite was added, with stirring. The reaction mixture turned green and gradually became lighter in color. After 30 min, 15 ml of water was added. The light gray precipitate was filtered off and washed with water, yielding 0.282 g of moist VI. The moist VI was purified by dissolving in a mixture of 12 ml of acetone and 7 ml of water, treating with charcoal and sodium hydrosulfite, and filtering. The filtrate was poured into distilled water, preheated to 60°C. The suspension was stirred for 20 min and cooled to 20°C. The precipitate was filtered off, washed with water and dried, yielding 0.261 g of VI, mp 283-285°C. The radiochemical yield was 10.3%, calculated from I. The specific activity was 30 mCi/g.

The radiochemical purity of VI was determined chromatographically on Silufol in the system methanol—chloroform (1:3) using a radiation detector. The radiochemical purity of VI was 99% (R_f 0.93).

[^{14}C]Riodoksol (VII). To a solution of 2.9 g of iodine monochloride in 3.3 ml of concentrated hydrochloric acid was added 12 ml of water, and the mixture cooled to 20°C. A solution of 0.655 g of III (specific activity 44 mCi/g) in 7 ml of 2.5% hydrochloric acid was added dropwise, with constant stirring. The addition rate was such that the temperature did not rise above 25°C. After 1 h the reaction mixture was diluted with 50 ml of water and allowed to stand for 12 h in the refrigerator. The residue was filtered off, washed with water and dried, yielding 2.35 g of impure VII. The product was purified by solution in 10 ml of ether and treatment with a 5% solution of sodium hydrosulfite until the red color disappeared. The ether solution was decanted and dried with anhydrous sodium sulfate. The ether was distilled off and the residue dissolved in 30 ml of boiling carbon tetrachloride. The solution was treated with 0.1 g of charcoal and filtered hot. The filtrate, on cooling to 10°C, deposited pale rose acicular crystals which were filtered and dried, yielding 1.13 g of product. A second recrystallization, from 15 ml of carbon tetrachloride yielded 0.697 g of VII, mp 157-158°C. The specific activity was 8.7 mCi/g. The radiochemical yield was 20.8%, calculated from III. The radiochemical purity of VII was determined chromatographically on Silufol in the system diethyl ether—petroleum ether (1:1) using a radiation detector. The chromatogram had one active spot (R_f 0.5), identical by the radiation detector and by UV light.

LITERATURE CITED

1. A. N. Grinev, M. Ya. Kraft, G. M. Borodina et al., Khim.-Farm. Zh., No. 9, 61 (1970).
2. A. N. Grinev, V. I. Shvedov, E. N. Sytina, et al., USSR Inventor's Certificate No. 495299, Otkrytiya, No. 46, 56 (1975).
3. A. L. Mikerina et al., British Patent No. 1430726, Izobr. rubezh., No. 9, 12 (1976).
4. A. A. Spryskov and S. P. Starkov, Zh. Obshch. Khim., 27, 2780 (1957).
5. A. P. Shestov and N. A. Osipova, Zh. Obshch. Khim., 26, 2005 (1956).
6. J. Stenhouse, Justus Liebigs Ann. Chem., 163, 183 (1872).
7. M. Ya. Kraft, G. M. Borodina, E. N. Sytina et al., USSR Inventor's Certificate No. 347328, Ref. Zh. Khim., No. 8N253P (1973).