[^{3}H]NONAKHLAZIN

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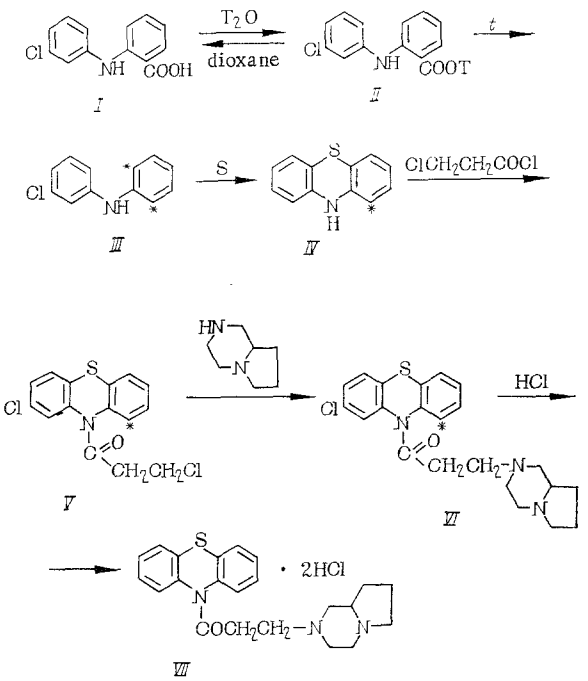
The preparation nonakhlazin [1], which possesses spasmolytic and coronary dilating action, has been synthesized with a labeled atom (tritium) in the phenothiazine ring.

Nonakhlazine is the dihydrochloride of 10'-[β-(1,4-diazabicyclo-[4,3,0]nonanyl-4)-propionyl]-2-chlorophenothiazine. We used a known method [2] to introduce the labeled atom by decarboxylating N-(m-chlorophenyl)anthranilic [^{3}H]acid with the tritium atom in the carboxyl group. The indicated acid was obtained by simple exchange with tritiated water (the cheapest labeled raw material) in dioxane. On closing the phenothiazine ring with sulfur, half of the introduced tritium was separated in the form of [^{3}H]hydrogen sulfide. However, using tritiated water of high specific activity, we obtained the required product, also extremely highly radioactive, by the scheme



EXPERIMENTAL

N-(m-Chlorophenyl)anthranilic [^{3}H]Acid (II). In a 100-ml flask (I) (10 g) and absolute dioxane (50 ml) was placed. After complete solution tritiated water (0.8 g) of specific activity 92 Ci/g was added. The total activity of the starting material was 73.5 Ci. After storing for 1 day, the dioxane and water were distilled off. The distillate, containing a large portion of the introduced activity, may be reused.

[^{3}H]Chlorodiphenylamine (III). A thermometer was immersed in the semiliquid mass which was heated at 250°C for 2.5 h. After evolution of carbon dioxide gas, III was obtained as a brownish-colored liquid.

[^{3}H]2-Chlorophenothiazine (IV). Sulfur (1.33 g) and crystalline iodine (0.1 g) were added to III. The mixture was heated at 170-175°C and shaken periodically for 1 h. The isolated [^{3}H]hydrogen sulfide was absorbed in alkaline solution. The mass was cooled and hexane (25 ml) was added. On trituration, IV crystal-

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lized. It was filtered off, washed with hexane (20 ml), then with absolute isopropyl alcohol (twice with about 5 ml), and crystallized from absolute isopropyl alcohol with addition of carbon. After filtration and drying IV (1.56 g) was obtained as a gray powder of mp 193-198°C. Specific activity was 0.3 Ci/g; total activity 4.68 Ci.

10-(β-Chloropropionyl)-2-chlorophenothiazine (V). Into a 30-ml flask IV (1.51 g; 4.55 Ci), absolute benzene (12 ml), and β-chloropropionyl chloride (0.8 ml) was placed. The solution was boiled under reflux for 2 h. The solvent was then distilled off to dryness. The residue was dried in vacuum at a residual pressure of 60 mm on a boiling water bath, absolute isopropyl alcohol (20 ml) and activated carbon were added, the mixture boiled for 10 min, filtered, and the solution cooled in an ice bath. The solid which separated was filtered off, washed with cold absolute isopropyl alcohol (twice with about 3 ml), and with hexane (three times with about 5 ml). After drying, (1.75 g) was obtained having mp 110-112°C [3]. The yield was 83.5% calculated on IV.

[^{3}H]Nonakhlazin (VII). Compound V (1.75 g) was dissolved with heating in absolute toluene (10 ml) in a 30-ml flask. Diazabicyclononane (1.4 ml was added to the solution and the mixture boiler under reflux for 3 h. The solution was cooled, washed with distilled water (three times with about 10 ml), and the reaction product extracted with 10% hydrochloric acid (three times with about 7 ml). Carbon was added to the aqueous extract, the mixture stirred for 5 min, filtered, and a 40% aqueous solution of sodium hydroxide added to strongly alkaline reaction. In this way VI separated in a precipitate as a white viscous mass. This was extracted with ether (three times with about 10 ml), the ether solution dried with anhydrous sodium sulfate, and VI was isolated by adding an ether solution of hydrogen chloride. The solid was filtered off, washed with dry ether dissolved in methanol (25 ml), carbon was added, the mixture was stirred for 5 min, filtered, and dry acetone (40 ml) poured in. The mixture was kept in the refrigerator for 1 day, after which dry ether (50 ml) was added, the white solid was filtered off, and washed on the filter with dry ether. Compound VII was obtained as a white powder of mp 215-218°C [4]. Specific activity was 1.35 Ci/g; total activity 2.0 Ci. Radiochemical yield was 43.9% calculated on IV.

Radiochemical analysis of [^{3}H]nonakhlazin was carried out by checking a chromatogram on Silufol in the system ethyl acetate–acetic acid–water (10:4:5); R_f 0.4. No radiochemical impurities were detected in the preparation. Its radiochemical purity was 100%.

Chemical analysis was carried out by comparing the molar extinction in the UV spectrum at $\lambda = 262$ nm with a chemically pure specimen. The chemical purity of [^{3}H]nonakhlazin was 98.3%.

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