## SYNTHESIS OF CARBON-14-LABELED 9-[2-(4-PYRIDYL)ETHYL]-3.6-DIMETHYL-1.2.3.4-TETRAHYDRO- $\gamma$ -CARBOLINE

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We have previously shown that several derivatives of tetrahydro- $\gamma$ -carboline, which have a pyridylethyl substituent in the 9-position, have a broad spectrum of pharmacological actin [1-3]. Carbon-14labeled 9-[2-(4-pyridyl)ethyl]-3 (C<sup>14</sup>), 6-dimethyl-1,2,3,4-tetrahydro- $\gamma$ -carboline (XI) was synthesized via the Fischer reaction from 1-methyl C<sup>14</sup> -4-piperidone (V) and 4-[N-amino-2(p-tolylamino)ethyl]pyridine (X) in order to study its distribution and metabolism in animal organisms.

The starting material for preparing the labeled preparation was  $C^{14}$ -methylamine hydrochloride (II); V was synthesized in one step without isolation of the intermediate products in order to decrease the loss in radioactivity.



Compound X was obtained via the following scheme:



Compound XI was subjected to qualitative chromatographic analysis on paper and on a thin layer of aluminum oxide, in conjunction with radio autography, in order to verify the radiochemical purity. The chromatograms were developed in UV light. A sample of unlabeled XI was used as a reference spot. Carbon-14-labeled XI has  $R_f \ 0.52$  on aluminum oxide in a benzene-absolute alcohol (10:1) system. The chromatogram and radio autogram of XI  $\cdot$  2HCl on paper in an n-butynol-acetic acid-water (10:1:10) system indicated the presence of only one component ( $R_f \ 0.69$ ), viz., carbon-14 labeled XI.

The results of preliminary pharmacological investigations on laboratory animals indicated that a single dose of 20 mg/kg is partially isolated unchanged from the urine and in the form of a metabolite (R<sub>f</sub> 0.41). The detection of  $C^{14}O_2$  in the exhaled air indicates that the preparation undergoes N-demethylation in the animal organism.

Detailed pharmacological investigations will be published separately.

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## EXPERIMENTAL

<u>1-Methyl( $C^{14}$ -piperidone (V)</u>. Carbon-14-labeled methylamine hydrochloride (0.606 g) was added to a solution of ice-cooled sodium methoxide obtained from 0.2 g of sodium and 5 ml of absolute methanol. The flask was sealed with a stopper and allowed to stand at room temperature for 2 h. Freshly prepared methyl acrylate (9 ml) was then added dropwise to the mixture with cooling and stirring, and the mixture was allowed to stand in the dark for 4 days. Next, a solution of 1.274 g of methylamine in 8 ml of absolute methanol was added to the ice-cooled mixture, and the resulting mixture was allowed to stand for another 4 days. The precipitated sodium chloride was filtered and washed with methanol. The solvent was removed, and the residue was cyclized with 1 g of powdered sodium metal in 10 ml of dry toluene. The next day, 50 ml of 20% hydrochloric acid was added to the solution, and the mixture was refluxed for 3 h. Water was removed in vacuo to one half the original volume, and the mixture was neutralized with cooling with concentrated sodium hydroxide. The oil which separated was extracted with ether, and the ether extract was dried with anhydrous sodium sulfate. After removal of the solvent, the residue was distilled in vacuo to give 2.2 g (39%) of V with bp 55-56° (11 mm). According to [4], V has bp 56-59° (14 mm).

 $\frac{4-[2-(p-Tolylamino)ethyl]pyridine (VIII). A mixture of 64.2 g of p-toluidine, 69.3 g of 4-vinylpyridine, and 3.6 g of glacial acetic acid was refluxed for 3 h at 130°. The excess 4-vinylpyridine was removed in vacuo, and the residue was distilled in vacuo to give 84 g (66%) of VIII with bp 195-200° (1-2 mm) and n<sup>20</sup><sub>D</sub> 1.5970. According to [5], VIII has n<sup>20</sup><sub>D</sub> 1.5969.$ 

4-[N-Nitroso-2-(p-tolylamino)ethyl]pyridine (IX). Sodium nitrite (36.5 g) in 100 ml of ice water was added with stirring to a solution of 84 g of VIII in 530 ml of 10% hydrochloric acid cooled to -2 (-6°). The mixture was then stirred for 1 h under the same conditions and made alkaline with sodium carbonate. The precipitate was filtered, washed with water, and dried to give 86 g (88%) of IX with mp 65-66° (from petroleum ether). Found %: N 17.25, 17.46. C<sub>14</sub>H<sub>15</sub>N<sub>3</sub>O. Calculated %: N 17.41.

<u>4-[N-Amino-2(p-tolylamino)ethyl]pyridine (X)</u>. Zinc dust (60 g) was added in small portions with vigorous stirring to a solution of 16.6 g of IX in 120 ml of 70% acetic acid and 30 ml of methanol cooled to -5 (-8°). Upon completion of zinc addition the mixture was stirred for 1 h at the same temperature. Unchanged zinc was filtered, and the filtrate was made strongly alkaline with concentrated ammonia and extracted with ether. The ether extract was dried over sodium sulfate. After removal of solvent the oil crystallized to give 8.1 g (50%) of X with mp 95° [from petroleum ether-benzene (5:1)]. The product formed a hydrazone with p-nitrobenzaldehyde with mp 172-173°. Found %: C 70.11, 70.06; H 5.63, 5.59.  $C_{21}H_{20}N_4O_2$ . Calculated %: C 69.97; H 5.60.

<u>Carbon-14-labeled 9-[2-(4-Pyridyl)ethyl]-3 C<sup>14</sup>, 6-Dimethyl-1,2,3,4-tetrahydro- $\gamma$ -carboline (XI).</u> A mixture of 3.4 g of X and 2 g of V was heated on a boiling water bath for 3 h. The hydrazone obtained was cyclized by addition of 30 ml of a 10% solution of dry hydrogen chloride in absolute alcohol. The next day, the precipitated ammonium chloride was filtered from the hot solution and washed with absolute alcohol. The filtrate was cooled, and the precipitated XI  $\cdot$  2HCl was filtered and dried to give 3.3 g (60%) of the hydrochloride with mp 222-223° (decomposition from absolute alcohol). The specific activity of the hydrochloride was 0.45  $\mu$ Ci. The free base had mp 103-105° (from heptane). The dipicrate had mp 203°. Found %: C 50.69, 50.46; H 4.14, 4.19; N 16.67, 16.65. Calculated %: C 50.32; H 3.83; N 16.51.

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