PREPARATION OF ^{14}C- LABELLED TRAZODONE HYDROCHLORIDE.

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Trazodone hydrochloride*, 2-{3-[(4-m-chlorophenyl)-1-piperazinyl] propyl} s-triazolo-[4,3-a]-pyridine-3(2H)-one hydrochloride is a new psycotropic drug derived from triazolopyridine[1] and has been extensively investigated in the pharmacological and clinical fields[2, 3, 4].

For the studies on metabolism of Trazodone hydrochloride in animal isotopically labelled form of the drug was required. The method for preparation of labelled Trazodone hydrochloride was planned under the following conditions : (1) Triazolopyridine ring is labelled with carbon-14, (2) The process of synthesis is carried out in a flask. The present paper deals with the synthesis of ^{14}C-labelled Trazodone hydrochloride [I], outlined in Fig. 1.

2-pyridylhydrazine [II] was synthesized according to the modified method reported by Fargher and Furness[5]. A mixture of 30 mg (0.50 mmole) of ^{14}C-urea with a specific radioactivity of (200 μCi/mg) and 55 mg (0.50 mmole) of 2-pyridylhydrazine purified by re-distillation was heated in a flask (20 ml volume) equipped with air condenser up to 235°C on oil bath and then the mixture was allowed to stand for 5 minutes at the same temperature. After cooling and adding 10 ml xylene to the reaction mixture, the solu-

* This name has been reported as the nonproprietary name in the Journal of the American Medical Association 211 : 1362 (1970).

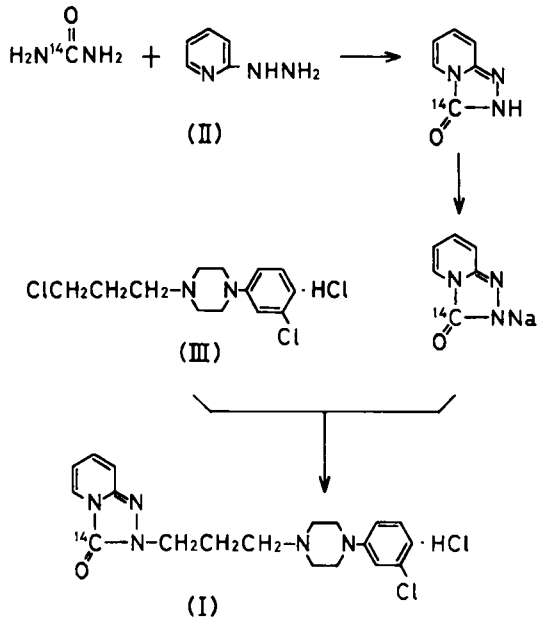

Fig. 1 Synthesis of ^{14}C-Trazodone Hydrochloride

tion was refluxed for approximately 10 minutes. Then, 100 mg of NaH (50 % powder in oil) was added to the solution following cooling, and the mixture was refluxed for 1 hour. 180 mg (0.66 mmole) of N-m-chlorophenyl-N'-γ-chloropropylpiperazine hydrochloride [III] was added to the solution and thereafter the mixture was refluxed for 15 hours with vigorous stirring on oil bath maintained at 160°C and then for 5 hours at 180°C.

After standing overnight, the precipitates were filtered and washed with xylene.

Following addition of washings to the filtrate, the xylene solution was charged on a silica gel column (Wako gel c-200 obtain-

ed from Wako Junyaky Co., 1.5 x 12 cm). The column was washed with approximately 50 ml of xylene at first and then eluted with cyclohexane - diethylamine (9 : 1).

The fraction which showed a strong fluorescence of blue-white color under 3650 Å was collected and evaporated under reduced pressure. After dissolving the residue in 5 ml of ethanol, the undissolved solid was filtered off. The ethanol solution was acidified by adding approximately 0.2 ml of conc. HCl, concentrated to appearance of crystals by evaporation and allowed to stand overnight at room temperature. The crystals were filtrated, washed with a small amount of ethanol and then dried over P_2O_5 in vacuo.

The product showed a single radioactive peak at the same position as that of the authentic Trazodone hydrochloride on the thin layer chromatograms using two kinds of solvents, respectively. The thin layer chromatography was carried out using Kieselgel (0.25 mm in thickness) with benzene - cyclohexane - diethylamine (4 : 5 : 1, Rf of Trazodone hydrochloride 0.65) and n-butanol - water - acetic acid (5 : 4 : 1, upper layer, Rf of Trazodone hydrochloride 0.60) as solvents and scanned using Aloka thin layer chromatogram scanner model TLC-2. The product, therefore, was confirmed to be pure Trazodone-3-^{14}C hydrochloride. 81 mg of Trazodone-3-^{14}C hydrochloride with a specific radioactivity of 27.3 μCi/mg was obtained in a yield of 37.0 % on the basis of ^{14}C-urea used.

The investigation on metabolism of Trazodone hydrochloride will be reported elsewhere.

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