aliphatischen Aminen mit drei gleichen Alkylresten brauchbar. Bei den notwendigen hohen Reaktionstemperaturen setzen allerdings Nebenreaktionen ein, wodurch ein kleiner Teil der ^{14}C-Aktivität verloren geht.

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Synthesis of 7-Chloro-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepine-5-^{14}C hydrochloride [1]

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7-Chloro-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepine-5-^{14}C hydrochloride, IX, a new benzodiazepine derivative with psychotropic activity was needed labelled with an isotope for metabolic studies, and we preferred incorporation of the isotope into the benzophenone moiety of the benzodiazepine, because it appears to be the most inert portion of the molecule, both chemically and metabolically. A label in this portion would permit most, if not all, metabolic changes to be followed.

The available synthetic routes ([2, 3, 4]) for the preparation of IX all have the disadvantage that a ^{14}C-labelled benzophenone would have to be prepared at the start of the synthesis by way of a low yield reaction ([5]) prior to construction of the seven-membered ring. In order to preserve isotopic material, the synthetic route outlined in Figure 1 was worked out.

Starting material V for the radiosynthesis was obtained by way of a four step sequence starting with *p*-chloroaniline (I). *p*-Chloro-*N*-methylaniline (IV) was prepared by tosylation of I, methylation of the tosyl-sodio derivative with dimethyl sulfate and removal of the tosyl group by strong acid hydrolysis. Aminoethylation ([6]) was carried out in good yield by treatment with ethyleneimine under aluminum chloride catalysis.

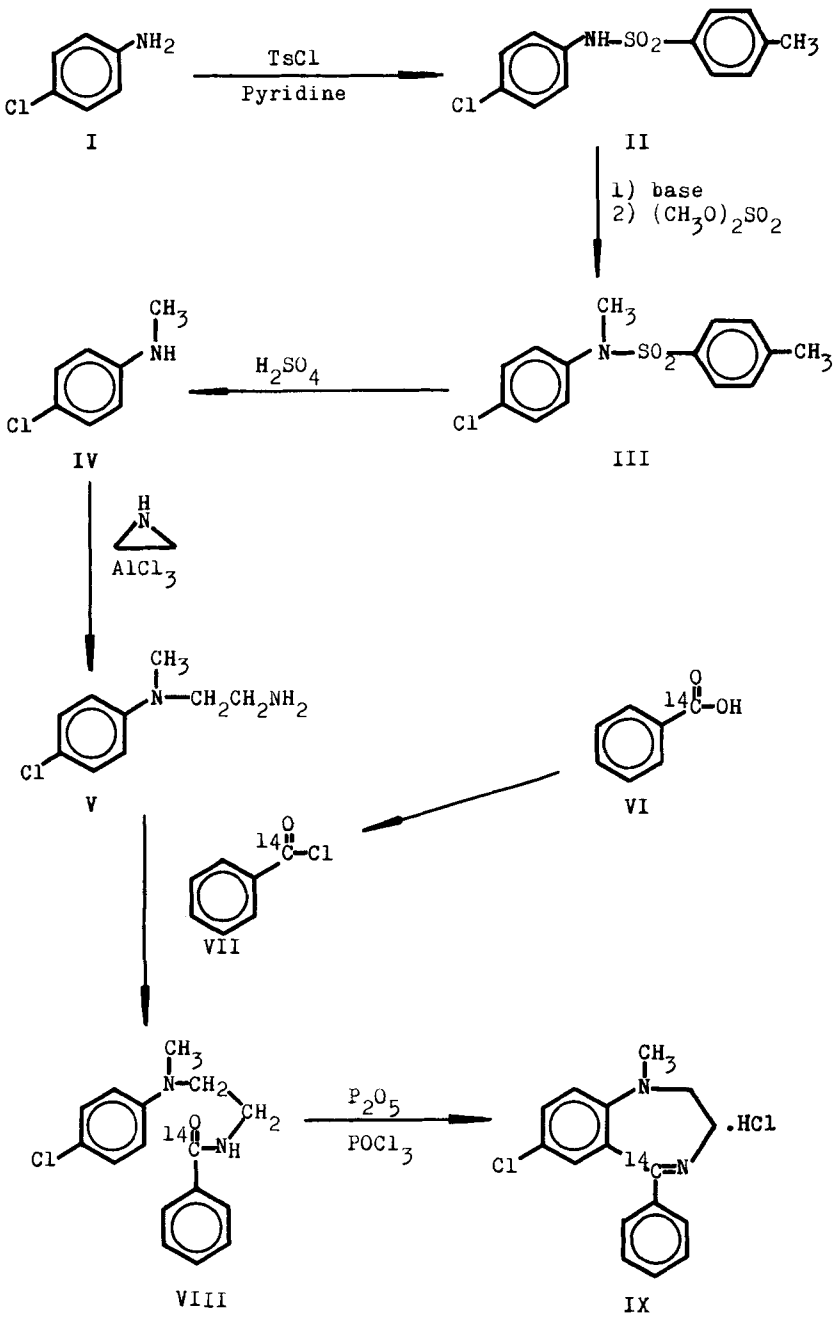
TsCl
Pyridine
I
II
1) base
2) $(CH_3O)_2SO_2$
H_2SO_4
IV
III
$AlCl_3$
V
VI
VII
VIII
IX
P_2O_5
$POCl_3$
.HCl

Figure 1

Benzoylation of V with benzoyl-7-^{14}C chloride in refluxing benzene yielded VIII in excellent yield. Its cyclization under Bischler-Napieralski conditions was best carried out with phosphorus pentoxide and phosphorus oxychloride, yielding 70 % of the benzodiazepine (IX).

N- (p-Chlorophenyl) -N-methyl-ethylenediamine (V).

p-Chloro-N-methylaniline (IV) was prepared according to published procedure from *p*-chloroaniline (I) [7].

To 13,3 g of aluminum chloride and 20 ml of dry benzene, in a 50 ml three-neck flask equipped with reflux condenser, dropping funnel and stirrer, was added 14.1 g (0.1 M) of *p*-chloro-N-methylaniline slowly and with cooling. After complete addition, the mixture was heated until reflux commenced and kept at that temperature for a short period. Freshly distilled ethyleneimine (4.3 g, 0.1 M) was then slowly distilled into the reaction vessel from a small flask attached to the former with a gas-inlet-tube by means of heating the flask with a hair dryer. The reaction vessel itself does not need to be heated since the ensuing reaction is sufficiently exothermic to maintain reflux. After the addition was complete, the reaction mixture was stirred for another thirty minutes and then poured on 200 g of ice contained in a 1,000 ml flask fitted with a condenser. Solid potassium hydroxide, 50 g, was added to the resulting solid in small portions, and the material went into solution. It was cooled and extracted three times with benzene. The combined organic extracts were dried over potassium hydroxide pellets and concentrated. The residue was distilled *in vacuo* through a ten-cm Vigreux column : a yield of 13.7 g (74 %), boiling point 126-127 °C at 0.05 mm Hg was obtained. Vapor phase chromatography analysis showed the compound to be 97.9 % pure. A small portion of the compound was redistilled and analyzed 98.6 % pure.

Anal. Calcd for $C_9H_{13}ClN_2$: C, 58.53; H, 7.10; N, 15.17; Found : C, 58.79; H, 7.02; N, 15.20.

N-(p-Chlorophenyl)-N-methyl-N'-benzoyl-7-^{14}C-ethylenediamine (VIII).

A mixture of 43.6 mg benzoic-7-^{14}C-acid containing 4.01 mC and 78.5 mg inactive benzoic acid (a total of 1 mM) were stirred and refluxed with 0.18 ml thionyl chloride (~2.5 mM) in 2.5 ml dry benzene for six hours. The reaction flask was then topped with a 15 cm Vigreux distilling head, 10 ml dry benzene added and the excess thionyl chloride distilled with the benzene. This was repeated with an additional 10 ml of dry benzene.

To the residue were added 5 ml dry benzene and 184 mg (1 mM) of N-(*p*-chlorophenyl)-N-methyl-ethylenediamine (V) dissolved in 5 ml dry benzene. A precipitate formed instantly. The mixture was stirred and refluxed for four hours. After cooling, 20 ml benzene and 10 ml 2N sodium hydroxide were added and thoroughly mixed. The organic layer was separated and washed with 10 ml water. The aqueous phases were re-extracted twice with ether.

The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated, yielding 276 mg (0.95 mM) crystalline amide, melting point 100-101 °C. This product was used in the next step without further purification. A 30 mg sample from a "cold" run was recrystallized twice from ethanol-water to give melting point 103-104 °C.

Anal. Calcd for $C_{16}H_{17}ClN_2O$: C, 66.55; H, 5.93; N, 9.70; Found : C, 66.78; H, 6.05; N. 9.87.

7-Chloro-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepine-5-^{14}C hydrochloride (IX).

The crude product from the benzoylation (VIII), 1.42 g (10 mM) of phosphorus pentoxide and 4m/ (43mM) of phosporus oxychloride were stirred at 110 °C for sixteen hours.

The reaction mixture was cooled and treated with 25 g of ice and 25 ml of 4N hydrochloric acid. The solution was extracted with ether and made basic with 10N sodium hydroxide. The organic free base was then extracted three times with methylene chloride and the extract dried. Removal of the solvent gave 188 mg of a yellow oil which was dissolved in 2 ml of methanol. Methanol (0.6 ml) containing 0.9 mM of hydrochloric acid was added and crystallization was induced by adding ether, yielding 186 mg of the hydrochloride, melting point 250-252 °C.

The compound was found to be radiochemically pure by thin layer chromatography on silica gel using chloroform-heptane-ethanol 10 : 10 : 1, showing only one spot and radioactivity peak,

The overall total yield was 60.6 % calculated on benzoic-7-^{14}C acid, the specific activity 13.5 μC/mg and the total activity obtained 2.51 mC.

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Synthesis of Carbon-14 and Sulfur-35 Labeled O-Ethyl-S-Phenyl-Ethyl-Phosphonodithioate

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0-Ethyl-S-phenyl-ethyl-phosphonodithioate *, a candidate broad spectrum insecticide [1], was labeled in the ethoxy moiety with carbon-14 and in the thiophenyl moiety with sulfur-35 to facilitate residue and metabolism studies.

O-1-^{14}C-ETHYL-S-PHENYL-ETHYL-PHOSPHONODITHIOATE

S-Phenyl-ethyl-phosphonochloridothioate, 0.34 ml (430 mg or 1.82 mmole) was added dropwise with stirring to a suspension of 122.4 mg (1.8 mmole) of sodium ethylate, having a specific activity of 5.75 mC per mmole, in anhydrous ether at —7° C. The reaction mixture was stirred and allowed to warm to room temperature over a period of one hour. The resultant mixture was washed to pH-7 with four 1.5 ml portions of distilled water. The product was dried over magnesium sulfate and filtered into a 25 ml pear-shaped flask. The volume was adjusted to 10 ml. A one λ sample of this solution was spotted on a 50 cm × 100 cm Brinkmann thin layer chromatography plate, precoated with a 250 micron layer of silica gel F_{254}. Authentic O-ethyl-S-phenyl-ethyl-phosphonodithioate was spotted on the same plate and the co-chromatogram developed with hexane/chloroform 60/40 for a distance of 5 cm. Visualization with N,2,6-trichloro-*p*-benzoquinoneimine (TCQ) showed two minor impurities. The plate was exposed to Kodak no-screen medical X-ray film for thirty minutes. Development of the radioautograph disclosed only one spot. Ether was evaporated from the solution yielding 368 mg of product, 83 % of theory.

* Dyfonate ® : registered trademark of Stauffer Chemical Company.