NOTES

PREPARATION OF GENERALLY AND SPECIFICALLY LABELLED PHENCYCLIDINE

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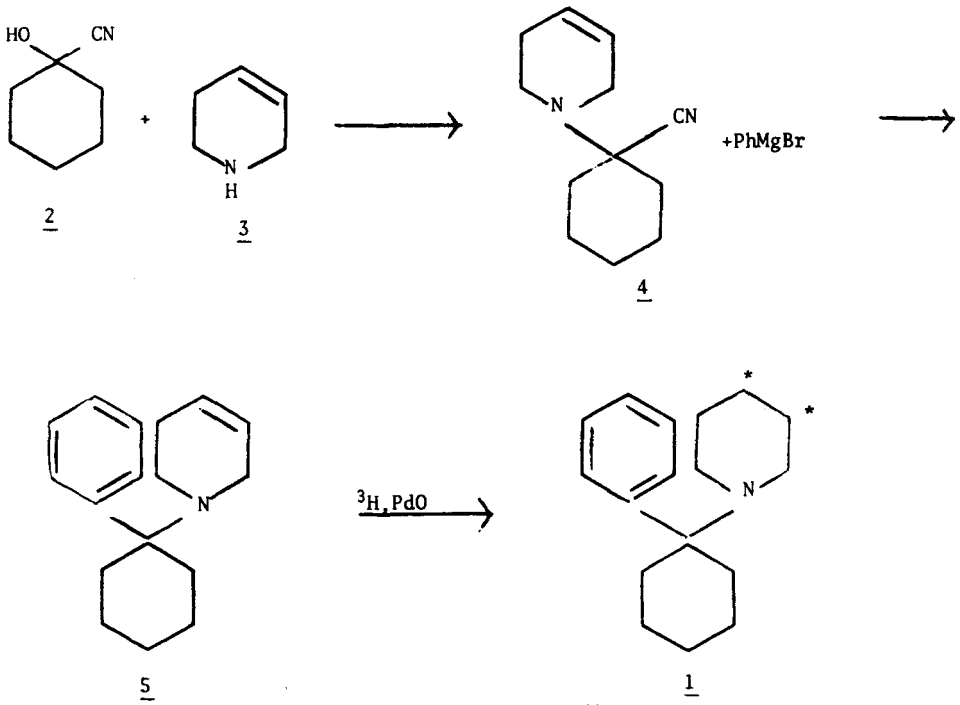
Radioactive phencyclidine 1-(1-phenylcyclohexyl)piperidine 1 has been required for physiological and radioimmunoassay studies[1] on this pharmacologically important compound[2].

Phencyclidine generally labelled with tritium (1G) has been obtained by the "in situ" tritiation procedure (3,4) described in Experimental. The specific activity was 3.77 Ci/mmol.

In order to obtain 1 of higher activity the following route was employed:



2 3 4 5 1

Condensation of cyclohexanone cyanohydrin 2[5] with 1,2,5,6-tetrahydropyridine 3 produced 1-(1,2,5,6-tetrahydropyridino)cyclohexanecarbonitrile 4 in 84% yield (the reported one step Strecker synthesis from cyclohexanone, 3.HCl and KCN gave only 33% yield[6]). Phenylmagnesium bromide and 4 yielded 1-(1-phenyl-

cyclohexyl)-1,2,5,6-tetrahydropyridine 5 which in turn was catalytically reduced with tritium to phencyclidine 1 labelled at positions 3 and 4 of the piperidine ring, and having specific activity 23.75 Ci/mmol.

EXPERIMENTAL

The reactions involving tritium gas were performed in a capillary glass system connected to a vacuum manifold[7].

Chemical purity was determined by UV (Perkin-Elmer 402 Ultra-Violet and Visible Spectrophotometer) and by analytical t.l.c. (pre-coated silica gel F_{254} plates, 0.25 mm, Merck).

Radiochemical purity was controlled by scanning the radio-chromatogram of the t.l.c. plates (Berthold, Dunnschicht Scanner·II, Model 2722). The total and specific activity were measured by liquid scintillation counting (Packard, Tricarb, Model 3004). NMR spectra were taken on a Jeol C-60-HL Instrument.

Phencyclidine -T (G)

12.4 mg (0.1 mmol) of PdO catalyst was added to a solution of 24.0 mg (0.1 mmol) phencyclidine[8] in 0.4 ml methanol. The reaction vessel (about 10 ml volume) was frozen with liquid nitrogen and air evacuated to a residual pressure of 10^{-2} mm Hg. The reaction system was filled twice with nitrogen gas, evacuated, and 20 Ci of tritium gas were transferred into the reaction vessel. The system was allowed to come back to ambient temperature and the suspension was vigorously stirred by a glass covered magnetic stirrer.

The reaction was stopped after 3.0 Ci (0.05 mmol) of tritium gas had reacted with the catalyst (20 min). The solution was then frozen and the residual tritium evacuated. The solvent and other possible high vapor pressure compounds were separated by cryo-sublimation at room temperature. To discard the tritium labile atoms, the crude reaction product was washed twice with 5 ml methanol which were separated by cryo-sublimation. The tritiated phencyclidine was then dissolved in 2 ml methanol and filtered through a pre-filter Millipore. The purification was performed by preparative silica gel t.l.c. (2 mm, Merck) developed in methanol. The product was extracted with ether and the solvent evaporated. The residue was dissolved in 0.1 N HCl and filtered giving 6.75 mg, 105 mCi of chemically and ra-

diochemically pure (over 99%) labelled phencyclidine with specific activity of 3.77 Ci/mmol.

The silica-gel t.l.c. plates were developed in the solvents systems: 1) ethyl acetate, cyclohexane (1:1); 2) methanol; 3) methanol, benzene (8:2).

1-(1,2,5,6-Tetrahydropyridino)cyclohexanecarbonitrile 4

120 g (0.96 mol) cyclohexane cyanohydrin 2[5] and 90 g (1.08 mol) of 3 (Fluka) were introduced into a 500 ml flask fitted with a condenser and a Dean-Stark receiver. The temperature rose from 20 to 54°. 200 ml benzene was added, the mixture heated, and the theoretical amount of water removed azeotropically during 2 hours. The solvent was evaporated, and the residue was distilled to give 154 g (84%) of 4. b.p. 170-175° (25 mm), n_D^{23} 1.5100, identical with a compound obtained earlier[6].

NMR (CCl_4)-5.5(d,2H,-CH=CH), 3.30(s,2H,-NCH_2CH=), 2.63(t,2H,-NCH_2CH_2), 2.1-1.6 (m,12H).

1-(1-Phenylcyclohexyl)-1,2,5,6-tetrahydropyridine 5

To PhMgBr (from 98g bromobenzene and 17.5 g Mg in 400 ml ether) 55g (0.29 mol) of 4 in 150 ml ether were added during 30 min. After heating for 2 hours the mixture was decomposed, the amine extracted with dil. HCl, liberated by addition of ammonia, reextracted with benzene, distilled at 125° (0.25 mm), and recrystallized from 95% ethanol. Yield 36 g (52%) of crystals m.p. 55-56°, litt.[6] 57-58°. NMR ($CDCl_3$)-7.04(s,5H, arom.), 5.5(s,2H,-CH=CH-), 2.88(s,2H,-NCH_2CH=), 2.22(t,2H,-NCH_2CH_2-), 2.1 - 1.4(m,12H).

1-(1-Phenylcyclohexyl)-3,4-T-piperidine (phencyclidine) 1

23.5 mg of 10% Pd/C catalyst was added to a solution of 25 mg (0.1 mmol) of 4 in 0.4 ml methanol. The general procedure is similar to that described for the labelling of phencyclidine -T(G). The reaction stopped after 8.6 Ci tritium gas had reacted with the substrate.

First purification by t.l.c. proved insufficient and a second final purification was needed (silica gel t.l.c. in methanol) to give 576 mCi of chemically and radiochemically pure tritiated 1 with a specific activity of 23.75 Ci/mmol.

REFERENCES

1. Kalir, A., Katz, E., Elkavets, R., Raveh, L. and Torten, M. - Abst. 25th IUPAC Congress, Jerusalem, 1975, p. 243.
2. Domino, E.F. - Int. Rev. Neurobiol., 6: 303 (1963).
3. Pri-Bar, I. and Buchman, O. - Chem. Commun., 1631 (1970).
4. Buchman, O., Pri-Bar, I., Shimoni, M. and Smoskowitz, L. - J. Label. Compounds, 10: 345 (1974).
5. Billimoria, J.D. and Maclagan, N.F. - J. Chem. Soc., 3067 (1951).
6. Kalir, A., Sadeh, Sh., Karoly, H., Shirin, E., Balderman, D., Edery, H. and Porath, G. - Israel J. Chem., 13: 125 (1975).
7. Wenzel, M. and Schulze, P.E. - in "Tritium Markierung", W. De Gruyter and Co., 1962, p. 19.
8. Kalir, A., Edery, H., Pelah, Z., Balderman, D. and Porath, G. - J. Med. Chem., 12: 473 (1969).

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