PREPARATION OF N-3-IODO (^{131}I) BENZENESULFONYL N'PROPYLUREA AND ITS TISSUE DISTRIBUTION.

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SUMMARY

The preparation, stability and tissue distribution of N-3-iodo (^{131}I)-benzenesulfonyl N' propylurea are described.

INTRODUCTION

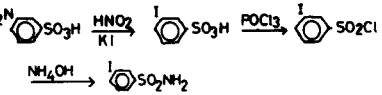
The pancreas is one of the organs for which a good radiopharmaceutical for external scanning purposes has not yet been prepared. The several attempts (1-17) to arrive at a suitable scanning agent for this endocrine organ have not yielded very fruitful results. The utility of ^{75}Se-L-selenomethionine as a pancreatic localizing agent has recently been questioned (18). Yet, in the absence of better imaging agents ^{75}Se-L-selenomethionine serves as the only compound to dilineate this gland.

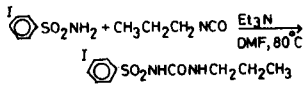
Various substituted arylsulfonyl-ureas are used clinically as oral hypoglycemic agents (19). The postulated mechanism of action of these substances is that they reduce the blood sugar by stimulating the insulin secretion from the beta cells of the pancreas (20). Utilising this premise Holcomb et al (17) prepared p-Iodopropamid and studied its distribution in several organs to evaluate its propensity as an agent for scanning the pancreas. It was noted by these workers that it did not concentrate in the

pancreas to a marked extent, and further in-vivo de-iodination was also observed.

It was postulated that if the iodine atom is present in the 3-position of the benzene ring, the resulting compound would be much more stable, and therefore, less susceptible to de-iodination both chemically and in-vivo conditions. N-3-iodobenzene sulfonyl N'propylurea, m-Iodopropamid for short, an isomer of the abovementioned compound, was synthesized (Scheme 1) from 3-iodobenzene-sulfonamide and n-propyliscoyanate, and the corresponding radioiodinated compound prepared by the chemical exchange of the compound with sodium iodide (^{131}I) in dimethyl sulfoxide as the solvent. Its tissue distribution was also studied. This new compound is chemically stable as compared to the para isomer which is thermally unstable, and undergoes much less in-vivo de-iodination. However, the concentration of this substance in the pancreas is not significant.

SYNTHESIS OF N-3-IODOBENZENE SULFONYL N'-PROPYL UREA; (m-IODOPROPAMIDE)





EXPERIMENTAL

The melting points are uncorrected. The chromatograms were obtained using Whatman No. 1 chromatographic paper strips and developed overnight in n-BuOH saturated with conc. NH_4OH (d = 0.91) - organic layer - as solvent (ascending); and the spots detected using UV light. The radiochromatograms were scanned for radioactivity by counting 5 mm cut strips in a Nuclear Chicago Automatic Gamma Sample Changer Assembly (model C 120-1 and 202).

The organs of the animals were counted in a well-type scintillation detector using a medical spectrometer.

1. 3-Iodobenzenesulfonamide (21)

20.7 g (0.12 mole) of metanilic acid was suspended in 50 mls . of conc. Sulfuric acid and placed in an ice-salt bath and cooled. A cooled solution of sodium nitrite (8.8g) in 35 mls of conc. sulfuric acid was added slowly with stirring and the temperature of the resultant solution was not allowed to exceed 5°C. Subsequently, a solution of potassium iodide (20.0g) was added and the solution was allowed to attain room temperature with constant stirring. The mixture was heated to boiling and the 3-iodobenzenesulfonic acid was salted out as the sodium salt, and recrystalised from hot water to yield 13.5 g (36.9%).

12.0 mls of phosphorus oxychloride was added to the dry sodium salt (5.1 g, 0.016 mole) and heated in an oil bath at 130° for 3 hours. It was cooled, and the mixture was poured into an ice-water slush (100 g), when the 3-iodobenzenesulfonyl chloride separated out as an oil. This was extracted with benzene and the benzene solution was treated with 100 mls. of aqueous ammonium hydroxide solution (50%), and the mixture was warmed for about 0.75 hour. The benzene layer was then allowed to evaporate off when 3-iodobenzenesulfonamide separated out on cooling. The crystals were filtered off, and recrystallized from hot water to give 4.33 g (84.9%) of the pure product. M.P. 155-156°C (lit. 152°). Rf = 0.79 - 0.82.

2. N-3-iodobenzenesulfonyl N'propylurea

849 mgm (3 mmole) of 3-iodobenzenesulfonamide was dissolved in 2.5 mls of redistilled dimethylformamide. To this was added 0.4 mls of n-propylisocyanate and 0.4 mls of triethylamine respectively. The mixture was heated with stirring at 80-85°C for 18 hours. It was cooled, and finally poured

into a 10% acetic acid solution and stirred for 2 hours; The N-3-iodobenzenesulfonyl N'propylurea precipitates out as a white solid. This was filtered, and crystallized from aqueous ethanol (50%) to furnish 570 mgm (51.6%) of the pure material. M.P. 126-127°. Rf = 0.73 - 0.76.

Elemental analysis:- Calculated C = 32.6%; H = 3.5%

Found C = 31.9%, H = 3.35%

3. N-3-iodo (^{131}I) benzenesulfonyl N'propylurea

The attempts to exchange the iodine atom for its radioactive label (^{131}I) using ethylene glycol as solvent at 150°C for 24 hours resulted in poor yields. Therefore, a more polar solvent, dimethylsulfoxide, was used.

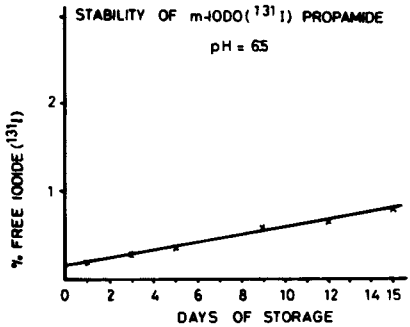
N-3-iodobenzenesulfonyl N'propylurea (16 mgms) was taken in 1.5 mls of dimethylsulfoxide in a 10 ml round-bottomed flask equipped with a condenser. 0.1 ml (10 mCi) of sodium iodide (^{131}I) (I-2,Na ^{131}I, in dilute alkaline sulfate solution - supplied by Isotope Division, B.A.R.C) was added and the flask heated at 150°C for 24 hours. Thereafter, it was cooled to room temperature and poured into water. The substance was extracted repeatedly with methylethyl ketone (or ether) and then dried over anhydrous sodium sulfate. The solution was decanted and the solvent evaporated off; and the compound was finally dissolved in dimethylsulfoxide- normal saline (1:2) solution, pH - 6, or else in dilute sodium hydroxide and the pH adjusted to 7. The radiochemical yield thus obtained was 40%.

The radiochemical purity was established by the paper chromatographic procedure when only one spot at Rf = 0.77 was obtained. Rf of free iodide (^{131}I) = 0.38.

Stability

Aliquots of 3-iodopropamid in ether or dimethyl-sulfoxide-saline solution, or in dilute sodium hydroxide maintained at 0°C and at room

temperature (28°C) were taken at different periods of time and chromatographed. Figure 1 gives the percentage of free iodide produced in the particular medium with respect to time. The amount of free iodide obtained on storage is less than 1% even after 15 days.



Tissue distribution

50 μc (0.1 ml) of the 3-iodo (^{131}I) propamid solution was injected intravenously into the tail vein of mice (Swiss strain). The mice were sacrificed at different intervals of time after removing the blood. Thereafter they were dissected and the different organs removed and counted. Table 1 gives the amount of radioactivity present in each organ in terms of the percentage of the administered dose. The predominant concentration was in the blood, intestines and in the liver, and to a negligible extent in the pancreas.

The chromatography of the contents of the bladder indicate that most of the activity is associated either as the parent compound, or a closely related metabolite (22,23) because the Rf value was very close to that of the original compound.

Acknowledgement

The technical assistance of Mr. R.B. Patkar in carrying out some of the animal work is greatfully acknowledged.

TABLE 1

ORGAN DISTRIBUTION OF m-IODO (^{131}I) PROPAMIDE IN MICE*

(Values expressed as percentage of administered dose)

TIME	0.5 hr	1 hr	2 hrs	4 hrs	6 hrs	8 hrs
ORGAN						
Spleen	0.47	0.485	0.30	0.12	0.06	0.11
Pancreas	0.65	0.565	0.245	0.125	0.085	0.07
Stomach	1.9	1.985	0.81	1.065	0.34	0.225
Intestines	9.84	8.47	5.05	3.045	2.79	1.515
Liver	6.305	5.755	1.81	0.78	0.49	0.26
Kidneys	2.48	2.085	1.19	0.29	0.15	0.115
Heart	1.035	1.075	0.475	0.12	0.08	0.045
Lungs	1.205	1.285	0.715	0.175	0.165	0.085
Thyroid	0.525	0.48	0.58	0.555	0.665	0.875
Blood	18.295	15.81	6.74	3.265	4.41	1.74

* Results are mean of 3 experiments with 2 mice in each case

References

1. Meschan, I., Quinn, J.L., Witcofski, R.L. and Hosick, T.A. -Radiology, 73: 62 (1959)
2. Sodee, D.B.- Nucleonics, 23: 56 (1965).
3. Norman, E. - Scand. J. Clin. Lab. Invest., 24: Suppl. 110 (1969).
4. Tubis, M. and Endow, J.S. - Int. J. Appl. Rad. & Isot. 19: 835 (1968).
5. Blau, M. and Bender, M.A.- Gastroenterology, 38:217 (1960).
6. Schatz, V.B., O'Brien, B.C., Chadduck, W.M., Kanter, A., Burger, A. and Sandusky, W.R.- J. Med. Pharm. Chem. 2: 444 (1960).
7. Mani, R.S. and Noronha, O.P.D. - Radiochem. Radioanal. Letters, 3: 119 (1970).
8. Wheeler, J.E., Lenkens, F.D.W. and Gyorgy, P.- Prot. Soc. Exp. Biol. Med., 70: 187 (1949).
9. Blau, M. and Maneke, R.P. - J. Nucl. Med., 2: 102 (1961).
10. Blau, M. - Biochem. Biophys. Acta, 49: 389 (1961).
11. Hammarstrom, L. and Ullberg, S.- Nature, 212: 708, (1966).
12. Hammarstrom, L., Hellman, B. and Ullberg, S.- Diabetologia, 3:340 (1967).
13. Ullberg, S. and Blomquist, L.- Acta Pharm. Suec., 5: 45 (1968).
14. Counsell, R.E., Smith, T.D., Di Guilo, W. and Beierwaltes, W.H. - J. Pharm. Sci. 57: 1958 (1968).
15. Varma, V.M., Beierwaltes, W.H., Lieberman, L.M. and Counsell, R.E. - J. Nucl. Med., 10: 219 (1969).
16. Hoyte, R.M., Lin. S.S., Christman, D.R., Atkins, H.L., Houser, W. and Wolf, A.P.- J. Nucl. Med., 12: 280 (1971).
17.a Holcomb, G.N., Boyd, C.M., Counsell, R.E., Beierwaltes, W.H., Szczesniak, R.A., Murty, D.R.K. and Bruno, G.A. -J. Pharm Sci. 60: 390 (1971).
17.b Lieberman, L.M., Beierwaltes, W.H., Boyd, C.M. - J. Nucl. Med. 13: 215 (1972).

18. Lundman, S., Polcyn, R.E. and Gottschalk, A.- Radiology, 100: 631 (1971).

19.a Campbell, G.D. - "Oral Hypoglycaemic Agents - Pharmacology and Therapeutics" - Academic Press (London and New York), (1969) pp 11, 31-33.

19.b "The Pharmacological Basis of Therapeutics". Goodman, L.S. and Gilman, A. The Macmillan Co. (New York) (1965), p. 1595.

20. Ibid (a) pp 10, 55, 97.
(b) p. 1594.

21. Langmuir, A.C. - Ber. 28: 93 (1895).

22. Gerstenberg, E., Hasselblatt, A., Schmitt, G.- Arch. Exp. Path. Pharmak, 231: 407 (1957).

23. "A Specialist Periodical Report - Foreign Compound Metabolism in Mammals" Vol. 1, The Chemical Society, London (1970) p. 404.