Syntheses and preliminary Distribution Studies of some Polycyclic Aliphatic iodides in the dog

By J. Ayoola Owoyale and Stephen S. Szinai*
**Department of Chemistry,*
University of Ilorin, Ilorin.

SUMMARY

Based on the hypothesis that radioiodinated 19-iodocholesterol, its ethyl andmethyl ethers and 3- iodocholestene owe their localization in the arenal glands to their polycyclic aliphatic properties, 4,8-bis(iodomethyl)tricyclo (5.2.1.0)–decane and 2-adamant-1-ylethyl iodide were synthesized, formulated and administered by intravenous injection to dogs. The dogs were sacrificed after 24 hours and three or four days and autopsies were performed. The radioactivity in the various organs and tissues were measured for each drug. The results indicated that these new drugs localized better in fat tissues and in most organs than in the adrenal and have therefore failed to support the above hypothesis.

INTRODUCTION

When 19-iodocholesterol was first synthesized, it was believed that it owed its adrenal localization on its being indistinguishable from endogenous cholesterol (1). But its isomer, 6 -iodomethyl-19-norcholest-5(10)-en-3 -ol (2), which should easily distinguishable from cholesterol, localized even better in the adrenals. 19-norcholesterol 3-acetyl ester (3) and more especially the 3-ethyl and 3-methyl ethers of 19-iodocholesterol (4) suggested that a hydroxyl group was not essential for adrenal localization. Since 3-iodo-5-cholestene (5) and a number of steroids based on the C-3 iodide (6) also localized in the adrenals, it was thought that these steroids could simply be regarded as iodide carriers on a polycyclic aliphatic backbone and therefore a steroid nucleus might not be essential for localization in the adrenals. This led to the syntheses and distribution studies of two polycyclic aliphatic iodides: 2-adamant-l-ylethyl (^{125}I) iodide (IVa) and 4,8-bis (^{125}I) iodemethyl)-tricyclo (5.2.1.0) decane (IVb).

MATERIALS AND METHODS

Chemistry

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are not corrected. Infrared (IR) spectra were recorded on a Beckmann infrared spectrophotometer Acculab 3. Mass spectrum (MS) was recorded on a Dupont Model 491 double beam instrument by direct probe. Qualitative thin layer chromatography (TLC) was run on Merck silical gel using cyclohexane-ethyl acetate (9:1) as the solvent system. Elemental analyses were performed by Midwest Microb, Indianapolis, Indiana. The major chemicals were obtained from Aldrich Chemicals.

The preparation of each iodide was achieved by the conversion of the corresponding alcohol to its tosylate followed by the reaction of the latter with sodium iodide as shown in Fig. 1. The tosylates and iodides however were not very stable and the iodides often started to decompose during their preparation.

2-Adamant-l-ylethyl tosylate (IIa). p. Toluene sulfonyl chloride (1.432 g) was added in portions with stirring to a solution of Ia (1.082 g)–prepared from 2-adamant-1-ylethyl acetate (7) in pyridine (3 ml) and anhydrous ether (1 ml) which was cooled down to temperatures between -5 and 10°C. The mixture was allowed to warm to room temperature and stirring continued for 4 hr, after which it was poured into ice-water and extracted with ether. The ether extract was washed twice with 10 per cent HCl once with 5 per cent $NaHCO_3$ and twice with water, dried (Na_2SO_4) and concentrated under vacuum. The resulting solid was recrystallized from pet. ether to give 1.54 g (76.7 per cent) of IIa as white cubes, m.p. 49-51°C; IR (KBr) 1600 (m), 1350 (s), 1185 (s) cm^{-1}; Anal calcd for $C_{19}H_{26}O_3S$: C, 68.22. H, 7.84;S, 9.59. found: C 68.36. H, 8.02; S, 9.55.

2-Adamant-l-ylethyl iodide (IIIa). A mixture of IIa (0.334 g) and sodium iodide (0.300 g) in ethyl methyl ketone (20 ml) was refluxed under N_2 for 2 hr. The reaction mixture was concentrated under vacuum to about 5ml and poured into ice-water and extracted with ether. The ether extract was dried Na_2SO_4) and concentrated to give a solid which was recrystallized from methanol to yield 0.26g (89.7 percent) of IIIa, m.p. 104-105°C; IR (KBr) abscence of absorption due to tosyloxyl and hydroxyl groups; MS: m/e 290 (M-I); Anal. calcd for $C_{12}H_{19}I$: C, 49.67; H, 6.60; 1, 43.74. found: C, 49.72; H, 6.72; I, 43.99.

4,8-Bis(tosyloxymethyl)tricyclo (5.2.1.0) decane (IIb). p-Toluene sulfonyl chloride (9.56 g) was added to a solution of the corresponding alcohol (Ib, 3.92 g) in pyridine (40 ml) that was cooled to 5°C. The mixture was kept in the refrigerator

for 48 hr. poured into ice-water and extracted with ether. The ether extract was treated as for IIa above to give a solid which was recrystallized from $CHCl_3$-H_2O to yield 3.1 g (30.7 per cent) of IIb, m.p. 87-90°C; IR (KBr) 1600, 1355, 1165 cm^{-1}; Anal. calcd. for $C_{26}H_{32}O_6S_2$: C, 61.88; H, 6.40; S, 12.71; found: C, 62.00; H, 6.44; S, 12.50.

4,8-Bis)iodomethyl)tricyclo (5.2.1.0) decane (IIIb). A solution of IIb (1 g) and sodium iodide (1.5 g) in ethyl methyl ketone (40 ml) was refluxed for 4 hr under N_2. The mixture was concentrated to ca 5 ml, poured into ice-water and extracted with ether. The ether extract was dried (Na_2SO_4) and concentrated to give an oil which was taken up in pet. ether and chromatographed over a florisil column and eluted with pet. ether. The appropriate fractions were combined (TCL), the pet. ether was removed udner vacuum to give 627 mg (76 per cent) of an oil, n_D^{25} 1.6125; IR (Neat): abscence of absorption due to tosyloxyl or hydroxyl group; m/e 416 (Mi): Anal. calcd for $C12H_{18}I_2$: C, 34.63; H, 4.36; I, 61.01; found: C, 34.66; H, 4.41; I, 61.15.

Synthesis of ^{125}I-labeled compounds (IVa,b). The synthesis of IVa is used as a typical example. Each product was worked up as described for the corresponding unlabeled iodide. A solution of 2-adamant-l-ylethyl tosylate (IIa, 190 mg) and sodium iodide-^{125}I (5.4 mCi) in ethyl methyl ketone (12 ml) was refluxed for 45 min under N_2 (TLC). Unlabeled sodium iodide (170 mg) was added and refluxing continued for two more hours. The reaction mixture was worked up as described for IIIa to give IVa (148 mg, 21 uCi/mg).

Formulation of radiolabeled compounds.

Using IVa still as a typical example, the product IVa (148 mg) was dissolved by slight warming in 95 per cent ethanol (12 ml), polysorbate-80 (90 drops) and enough 0.9 per cent saline solution to make up 150 ml of solution.

Distribution studies

A total of 5 Mongrel dogs each weighing between 18 and 30 kg was employed in these studies. Each dog received 50 ml of formulated drug (ca 60 uCi/kg) by injection into the foreleg vein. No further treatment or drug was given to these dogs. Three dogs received drug IVa and 2 others received IVb. One dog from each of the 2 groups was sacrificed 24 hr after drug administration by iv injection of lethal dose of sodium pentobarbital. The other 3 dogs were similarly sacrificed after 3 or 4 days. After the death of each dog, autopsy was performed and the organs–lung, liver, spleen, heart, kidney, testis, brain and adrenals–and samples of fat and muscle were collected and stored in formalin for one week to harden. About 3 block sections (ca 1 x 1 x 2.5 cm) were excised from each organ after thorough washing with water and blotting dry. All of the adrenal and samples of fat and muscle were also employed. Each section was placed in a plastic test-tube (1.5 x 15 cm) and the radioactivity in the sample was determined in a sodium iodide well crystal on Packard autogamma scintillation spectrophotometer, model 3001.

RESULTS AND DISCUSSION

The results of distribution of IVa and IVb are presented in Table 1. From the table, it will be noted that the adrenal concentration for IVa was lower than those of most organs and fat after 24 hours. The corresponding adrenal concentration for IVb was slightly lower than the concentrations in only the liver and fat. And even after three days the adrenal concentration of IVa was still lower than those in all organs and tissues except the brain. The relatively high concentration of IVa in the lung is worth noting especially since it indicated a two-fold increase from the 1st day whereas there was generally a decrease in the other organs and tissues. The tissue distribution of IVb at 4 days was similar to that after 24 hrs though these concentrations were much lower at four days. Unlike 19-iodocholesterol, it isomer, its 3-acetyl ester, its 3-ethyl and 3-methyl ethers and 3-iodo-5-cholestene which localize in the adrenal glands, these two new compounds localize better in body fat and poorly in the adrenals.

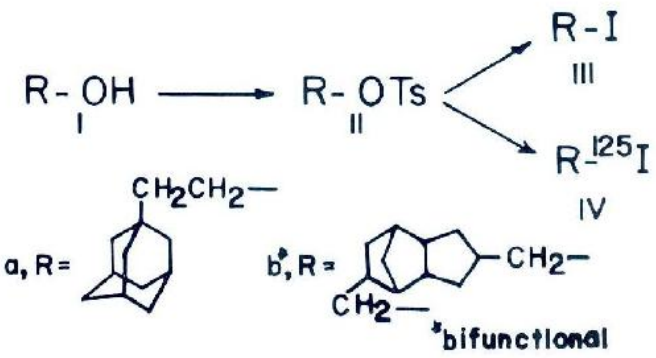
TABLE I

TISSUE DISTRIBUTION IN DOGS[a]

Tissue	One Day's Result IVa	IVb	Four Day's Result IVa[b]	IVb
Lung	9.02	10.67	18.19±6.24	1.80
Liver	12.59	19.76	8.82±1.46	5.17
Spleen	5.85	4.78	5.55±0.76	1.70
Heart	5.69	c	8.29±2.47	1.25
Kidney	8.90	7.31	9.41±5.18	1.78
Testis	–	4.73	–	–
Brain	3.35	5.93	1.23±0.11	0.65
Muscle	4.53	6.05	3.73±1.53	1.84
Fat	15.56	17.90	11.10±2.56	9.13
Adrenal	5.60	17.11	2.96±0.08	4.33

[a]Values represent DPM/mg of tissue
[b]Values represent DPM/mg ± SEM of tisse for 2 dogs after 3 days
[c]Sample lost.

In addition they have failed to demonstrate that the localization of the steroids above in the adrenal glands was due to their polycyclic aliphatic nature. Further work in this direction and probably some new hypothesis may be required to elucidate the structure-distribution relationship for drug localization in the adrenal glands.



REFERENCES

1. R.E. Counsell; V.V. Ranade; R.J. Blair; W.H. Beierwaltes and P.A. Weinhold. Steroids 16, 317 (1970).
2. M. Kojima; M. Maeda., H. Ogawa; K. Nitta and T. Ito. J.C.S. Chem. Comm. 47, (1975).
3. J.A. Owoyale. Steroids 38, 205 (1981).
4. J.A. Owoyale and S.S. Szinai. Steroids 37, 133 (1981).
5. J.A. Owoyale and S.S. Szinai. Acta Pharm. Suec. 18, 227 (1981).
6. W.H. Beierwaltes; D.M. Wieland; T. Yu; D.P. Swanson and S.T. Mosley. Seminars in Nuclear Medicine, Vol. VIII No. 1 (1978).
7. W.H.W. Lunn; W.D. Podmore and S.S. Szinai. J. Chem. Soc. 1658 (1968).