Potential Tumor or Organ Imaging Agents—31. Radioiodinated Sterol Benzoates and Carbamates

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A series of radioiodinated benzoate and carbamate esters of cholesterol and pregnenolone wherein the acyl moiety served as the carrier for radioiodine was synthesized and evaluated as potential imaging agents for the adrenal cortex. 2,6-Dimethyl-3-iodobenzoyl and N-(4-iodophenyl) carbamoyl groups were chosen as the acyl functionality in an attempt to provide esters resistant to in vivo hydrolysis. Tissue disposition studies in rats revealed that their biodistribution was determined by the attached sterol carrier—the cholesterol esters demonstrated significant uptake at 24 h in the adrenal whereas the corresponding pregnenolone derivatives showed only slight affinity for steroid-secreting tissues at this time.

Cholesterol is the principal metabolic precursor in the synthesis of adrenocortical hormones. This observation had led to the development of several radio-labeled cholesterol analogs as imaging agents for the adrenal cortex (Counsell et al., 1970; Hawkins et al., 1980; Maeda et al., 1975). Although 6β-[^{131}I]iodo methyl-19-norcholest-5(10)-en-3β-ol is the current agent of choice for adrenal imaging, it suffers from several limitations. The initial high uptake of this agent in tissues such as liver, colon and gall bladder requires that adrenal imaging be performed 4–5 days following i.v. adminstration in order to obtain a favorable adrenal to background ratio (Thrall et al., 1978). Moreover, the long biological half-life of this agent in the adrenals coupled with the relatively long half-life of ^{131}I ($t_{1/2} = 8$ days) leads to a significant radiation dose to this organ (Thrall et al., 1978). The development of an agent that would be rapidly and selectively taken up by the adrenals has been a major goal of our studies in that it would permit the use of the shorter-lived ^{123}I ($t_{1/2} = 13$ h). Employment of ^{123}I would not only reduce the radiation dose to the patient, but also provide a radiopharmaceutical suitable for single photon emission computed tomography (SPECT).

In previous papers we described the avid uptake displayed by a series of radioiodinated benzoate esters of cholesterol and pregnenolone into steroid-secreting tissues (adrenal and ovary) and the liver (Counsell et al., 1981; Seevers et al., 1982a, Van Dort, 1984). The retention of such esters in these tissues appeared to be related to their in vivo stability to hydrolysis (Seevers et al., 1982a,b; Van Dort et al., 1984). In particular, those analogs in which bulky groups were present in close proximity to the carbonyl of the ester functionality (e.g. the α-ethyl group in cholesteryl iopanoate and the ortho iodine in pregnenolone 2,3,5-triiodobenzoate) displayed appreciable retention in steroid-secreting tissues (Seevers et al., 1982a; Van Dort, 1984). In an effort to uncover other hydrolytically stable derivatives of pregnenolone and cholesterol the 2,6-dimethyl-3-iodobenzoate and 4-iodophenyl carbamate ester of these sterols were synthesized. This paper reports on the synthesis and preliminary biological evaluation of these ^{125}I-labeled steroid esters in rats.

Experimental

Melting points were obtained in open capillary tubes with a Thomas–Hoover apparatus and are uncorrected. NMR spectra were obtained on a Varian EM360 A spectrometer with $CDCl_3$ as solvent. Chemical shifts (δ) are reported in parts per milllion (ppm) downfield from tetramethylsilane, which was used as the internal stardard. Infrared spectra were obtained in the form of thin KBr wafers and recorded on a Perkin–Elmer 281 spectrophotometer. Elemental analyses were performed by Midwest Microlab Ltd, Indianapolis, Ind. All analyses

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(C, H, N, I) are within ±0.4% of the calculated values. Thin-layer chromatography (TLC) was done with Analtech preadsorbent glass-backed silica gel plates with fluorescent indicator. Chromatograms of radiolabeled compounds were scanned with a Vanguard 930 autoscanner. Column chromatography was done on silica gel from Grace Davison Chemical, Baltimore, Md. Cholesterol and pregnenolone were kindly supplied by G. D. Searle and Co., Skokie, Ill. Sodium ^{125}I was obtained from New England Nuclear, Boston, Mass. Tween 20 was obtained from Sigma Chemical Co., St Louis, Mo. Rats were obtained from Harlan Sprague Dawley, Inc., Hasslett, Mich. Chromatography (TLC) of tissue extracts were performed on plastic-backed silica gel plates with fluorescent indicator from Eastman Kodak Co.

2,6-Dimethyl-3-nitrobenzoic acid (1)

2,6-Dimethylbenzoic acid (3.0 g, 20 mmol) was nitrated according to a previously published procedure (Mandell et al., 1961) to afford 3.2 g (82%) of 1: m.p. 114–116°C (Benzene); lit. (Mandell et al., 1961) 111–115°C (ligroin); i.r. (KBr); 1700 cm^{-1} (C = 0); ^{1}H NMR (CDCl$_3$): δ 10.35 (s, l, COOH), 7.96 (d, 1, H-4, J = 9 Hz), 7.27 (d, 1, H-5, J = 9Hz), 2.58 (s, 3, 2-CH$_3$), 2.50 (s, 3, 6-CH$_3$).

2,6-Dimethyl-3-aminobenzoic acid (2)

A solution of 1 (2.65 g, 13.6 mmol) in absolute ethanol (150 mL) was treated with PtO$_2$ (0.26 g) and hydrogenated at 45 psi until the stoichiometric amount of H$_2$ was absorbed. The precipitated amine was isolated by filtration along with the catalyst and the residue reconstituted in boiling THF (400 mL). The catalyst was removed by filtration and the filtrate evaporated in vacuo. This provided a solid residue which was purified by washing with ice-cold THF (10 mL). Drying under high vacuum afforded 2.04 g (91%); m.p. 276–278°C (d); i.r. (KBr): 3100–2800 cm^{-1} (amine salt); 1615 cm^{-1} (C = 0); ^{1}H NMR (CDCl$_3$): δ 7.93–6.80(br s, 3, –NH$_3$, exch. with D$_2$O), 6.81 (d, 1, H-4, J = 8 Hz), 6.58 (d, 1, H-5, J = Hz), 2.10 (s, 3, 2-CH$_3$) 1.96 (s, 3, 6-CH$_3$). Anal. calc. for C$_9$H$_{11}$NO$_2$: C, 65.43; H, 6.71; N, 8.48. Found: C, 65.19; H, 6.93; N, 8.35.

2,6-Dimethyl-3-iodobenzoic acid (3)

A slurry of 2 (1.50 g, 9.1 mmol) in a mixture of concentrated H$_2$SO$_4$ (2.5 mL) and H$_2$O (5.0 mL) at 5°C (ice bath) was treated to the dropwise addition of NaNO$_2$ (0.63 g, 9.1 mmol) in H$_2$O (2.5 mL). Upon completion of the addition the clear yellow solution was maintained at 0°C for a further 2 h. The cold diazonium salt solution was then treated in one portion with a prechilled solution (0°C) of KI (1.50 g, 9.1 mmol) and I$_2$ (1.15 g, 4.6 mmol) in H$_2$O (2.5 mL). The reaction mixture was stirred for 16 h at room temperature and then warmed at 70°C for 0.5 h on the steam bath. The aqueous suspension was treated with solid NaHSO$_3$ (1.0 g), filtered, and

dried under high vacuum to afford 2.60 g of crude material. Column chromatography on silica gel with hexanes:EtOAc:HOAc (100:100:0.5) as eluant gave 2.1 g (83%) of analytically pure material, m.p. 115–117°C (d); i.r. (KBr): 1692 cm^{-1} (C = 0); ^{1}H NMR (CDCl$_3$): δ 10.62 (br s, 1, COOH), 7.87 (d, 1, H-4, J = 8 Hz), 6.83 (d, l, H-5, J = 8Hz), 2.56 (s, 3, 2-CH$_3$), 2.40 (s, 3, 6-CH$_3$). Anal. calc. for C$_9$H$_9$IO$_2$: c, 39.16; H, 3.28; I, 45.97. Found: C, 39.49; H, 3.38; I, 45.73.

2,6-Dimethyl-3-iodobenzoyl chloride (4)

A solution of 3 (1.5 mmol) in thionyl chloride (4.0 mL) was refluxed for 1.5 h under a nitrogen atmosphere. The solvent was evaporated in vacuo and the residual thionyl chloride was removed by azeotropic distillation with dry benzene (4 × 5 mL). Final traces of thionyl chloride were removed by drying the crude product overnight under high vacuum. This crude product was used for the synthesis of the sterol esters without further purification.

General procedure for synthesis of the sterol esters 5 and 6

A solution of the acid chloride 4 (1.5 mmol) in dry benzene (8 mL) was treated with the appropriate sterol (1.5 mmol) and triethylamine (0.167 g, 1.65 mmol) and refluxed under nitrogen for 16 h. The product was taken up in benzene (50 mL), washed with 0.5 N HCl (2 × 5 mL), saturated aqueous NaHCO$_3$ (1 × 50 mL), saturated brine (1 × 50 mL), and dried (MgSO$_4$). The solvent was evaporated to dryness under reduced pressure and the residue chromatographed on silica with EtOAc:hexanes (1:4) as eluant to afford the sterol ester. Analytically pure material was obtained by recrystallization from a suitable solvent.

Cholesteryl-2,6-dimethyl-3-iodobenzoate (5)

Yield of 64%; m.p. 162–164°C (acetone); i.r. (KBr): 1730 cm^{-1} (C = 0); ^{1}H NMR (CDCl$_3$): δ 7.70 (d, 1, Ph-H$_4$, J = 8.0 Hz); 6.70 (d, 1, Ph-H$_5$, J = 8.0 Hz); 5.40 (d, 1, H-6); 2.37 (s, 3, 2-CH$_3$); 2.25 (s, 3, 6-CH$_3$). Anal. calc. for C$_{36}$H$_{53}$IO$_2$: C, 67.07; H, 8.28; I, 19.68. Found: C, 66.88; H, 8.52; I, 19.70.

Pregnenolone-2,6-dimethyl-3-iodobenzoate (6)

Yield of 54%; m.p. 154–156°C (acetone); i.r. (KBr): 1728 cm^{-1} (ester C = 0), 1679 cm^{-1} (aceto C = 0); ^{1}H NMR (CDCl$_3$): δ 7.78 (d, 1, Ph-H$_4$, J = 7.8 Hz), 6.77 (d, 1, Ph-H$_5$, J = 7.8 Hz), 5.50 (d, 1, H-6), 4.96 (br m, 1, H-3), 2.40 (s, 3, 2-CH$_3$), 2.28 (s, 3, 6-CH$_3$), 2.15 (s, 3, 21-CH$_3$). Anal. Calc. for C$_{30}$H$_{39}$IO$_3$: C, 62.72; H, 6.84; I, 22.09. Found: C, 62.69; H, 6.73; I, 21.84.

General procedure for preparation of sterol carbamates

A solution of the sterol (1.0 mmol) and 4-iodophenylisocyanate (1.0 mmol) in dry benzene (15 mL) was refluxed for 16 h under a nitrogen atmosphere. The residue obtained following removal of the solvent

Table 1. Distribution of radioactivity at 0.5 and 24 h after i.v. administration of ^{125}I labeled sterol esters

Tissue	Cholesteryl benzoate (5)	Pregnenolone benzoate (6)	Cholesteryl carbamate (7)	Pregnenolone carbamate (8)
0.5 h				
Adrenal cortex	5.87 ± 0.51*	4.02 ± 0.54	6.57 ± 1.09	2.33 ± 2.32
Blood	7.20 ± 0.54	1.47 ± 0.10	3.18 ± 0.19	0.88 ± 0.04
Kidney	0.73 ± 0.14	0.63 ± 0.07	0.36 ± 0.07	0.53 ± 0.07
Liver	3.09 ± 0.48	1.51 ± 0.12	6.41 ± 0.56	0.69 ± 0.00
Ovary	6.41 ± 2.43	1.20 ± 0.24	3.45 ± 0.86	0.59 ± 0.10
Thyroid	1.56 ± 0.11	83.41 ± 27.89	3.13 ± 1.23	157.99 ± 38.65
24 h				
Adrenal cortex	25.58 ± 4.88	1.46 ± 0.32	11.32 ± 2.60	0.19 ± 0.04
Blood	1.17 ± 0.26	0.07 ± 0.00	0.50 ± 0.05	0.10 ± 0.04
Kidney	0.43 ± 0.08	0.08 ± 0.00	0.38 ± 0.04	0.09 ± 0.01
Liver	8.24 ± 1.07	0.33 ± 0.04	8.56 ± 1.19	0.15 ± 0.02
Ovary	30.86 ± 4.51	1.57 ± 0.16	10.15 ± 3.09	0.19 ± 0.04
Thyroid	31.96 ± 8.64	800.94 ± 321.23	70.30 ± 12.06	1399.12 ± 314.37

*Values expressed as % administered dose per gram of tissues ± SD (n = 3–4).

under reduced pressure was chromatographed on a silica gel column with EtOAc:hexanes (1:4). Recrystallization from acetone afforded analytically pure material.

N-(4-Iodophenyl)cholesteryl-3-carbamate (7)

Yield of 94%; m.p. 176–177°C; i.r. (KBr): 1728 cm^{-1} (C = 0). ^{1}H NMR (CDCl$_3$): δ 7.68 (d, 2, Ph–H); 7.22 (d, 2, Ph–H); 6.58 (s, 1, NH); 5.43 (br m, 1, H-6); 4.62 (br m, 1, H-3). Anal. calc. for C$_{34}$H$_{50}$INO$_2$: C, 64.64; H, 7.98; N, 2.22. Found: C, 64.84; H, 7.89; N, 2.12.

N-(4-Iodophenyl)pregnenolone-3-carbamate (8)

Yield of 93%; m.p. 225–227°C (d) i.r. (KBr): 1732 cm^{-1} (carbamate C = 0) 1694 cm^{-1} (aceto C = 0); ^{1}H NMR (CDCl$_3$): δ 7.66 (d, 2, Ph–H); 7.20 (d, 2, Ph–H); 6.64 (s, 1, NH); 5.42 (br m, 1, H-6); 4.62 (brm, 1, H-3); 2.15 (s, 3, 21-CH$_3$); 1.05 (s, 3, 19–CH$_3$); 0.63 (s, 3, 18-CH$_3$). Anal. calc. for C$_{28}$H$_{36}$INO$_3$: C, 59.89; H, 6.46; N, 2.49. Found: C, 59.80; H, 6.61; N, 2.31.

Radioiodination with Na^{125}I

Radioiodination was accomplished by isotope exchange with Na^{125}I in pivalic acid as previously described (Weichert *et al.*, 1986). Purification of the radioiodinated compounds was achieved by column chromatography on silica gel using hexanes:EtOAc (5:2) for elution of the benzoate esters and hexanes: EtOAc (3:1) for elution of the carbamate esters. Radiochemical yields were 78, 55, 58 and 50% for ^{125}I labeled 5, 6, 7 and 8, respectively. The radiochemical purity of the radioiodinated esters was > 95% as determined by radio-TLC analysis. Specific activities of the labeled esters 5, 6, 7 and 8 were 0.50, 0.32, 0.37 and 0.15 Ci/mmol, respectively.

Biodistribution studies

The radiolabeled compounds were dissolved in benzene and Tween 20 and added. The benzene was evaporated under a stream of nitrogen and physiological saline was added. Any remaining benzene was removed by a stream of nitrogen until a clear solution

(2 – 3% in Tween 20) resulted. The radiolabeled compound, thus solubilized, was administered intravenously to adult female Sprague–Dawley rats weighing 190–240 g. Three to four rats were used for each compound at each time period, and the dose ranged between 5 and 15 μCi per animal. The rats were killed by exsanguination under ether anesthesia at 0.5 and 24 h and the major organs were removed and blotted free of excess blood. Large organs were minced with scissors. Weighed samples of tissue were placed in cellulose acetate capsules and counted (81–85% efficiency) in a well scintillation counter (Searle 1185). The results are summarized in Table 1.

Analysis of extracted radioactivity from plasma and tissues

Radioactivity was extracted from plasma, adrenal cortex and liver using the procedure described previously (Van Dort *et al.*, 1987). A system of benzene:ethyl acetate (9:1) was employed for TLC analysis of the lipid extracts. The plates were then developed with the appropriate solvent system for 14.5 cm and air-dried. The plates were cut into 1 cm strips starting 0.5 cm below the origin and continuing to the solvent front. Each strip was placed in a counting tube and assayed for radioactivity. Each unlabeled ester was cochromatographed with the radioactive samples and visualized with iodine vapor to serve as a reference standard.

Results and Discussion

The synthesis of the 2,6-dimethyl-3-iodobenzoate esters of cholestrol and pregnenolone (5 and 6) is outlined in Scheme 1. Nitration of commercially available 2,6-dimethylbenzoic acid afforded the 3-nitro derivative (1) which was reduced by catalytic hydrogenation over PtO$_2$ to the corresponding amino analog (2). Diazotization of 2 and treatment of the diazonium intermediate with KI/I$_2$ afforded 2,6-dimethyl-3-iodobenzoic acid (3). Our initial attempts at preparing the sterol esters of 3 by a direct dicyclohexylcarbodiimide (DCC) catalysed esterification were unsuccessful probably due to increased steric
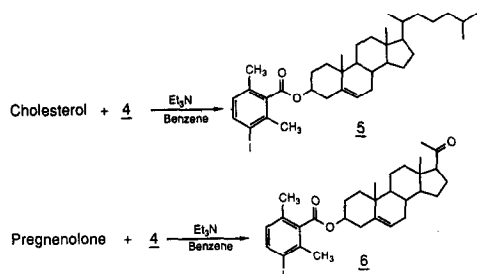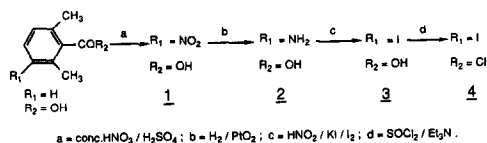
Scheme 1
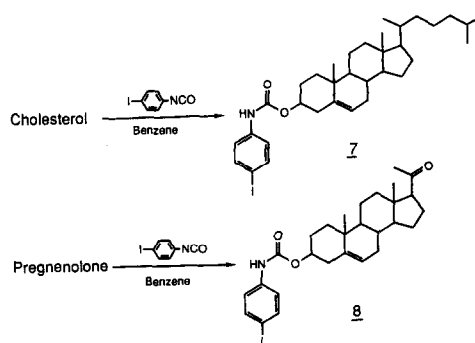
Scheme 2

hindrance afforded by the 2,6-dimethyl groups. However, these esters were prepared sucessfully by treatment of the appropriate sterol with the acid chloride 4, in the presence of triethylamine.

Synthesis of the iodophenylcarbamate esters of cholesterol and pregnenolone was achieved directly as shown in Scheme 2 by refluxing equimolar amounts of the appropriate sterol and 4-iodophenyl isocyanate. Radioiodination of these sterol esters was achieved by isotopic exchange in pivalic acid as previously described (Weichert et al., 1986). The radiolabeled compounds were solubilized in normal saline with the aid of Tween-20 prior to i.v. administration via the tail vein to female Sprague–Dawley rats. Groups of animals were sacrificed at 0.5 and 24 h and tissues were analyzed in a γ-counter for uptake of radioactivity. The results of these studies are summarized in Table 1. Although a total of twelve tissues were analyzed, only those tissues displaying

high concentrations of radioactivity are tabulated.

Analysis of the biodistribution profiles of these compounds revealed that their tissue disposition was determined by the attached sterol carrier. Similar findings have been reported by us previously (Seevers et al., 1982a: Van Dort et al., 1987). For example, both the carbamate and benzoate esters of cholesterol showed an ability to localize in the liver and steroid-secreting tissues. This accumulation was significant at 24 h with respect to the cholesteryl ester 5 which showed an uptake of over 25 and 30% of the injected dose per gram of tissue in the adrenals and ovaries, respectively. In the case of the carbamate ester 7, the adrenal uptake at 0.5 h was similar to 5, but the level at 24 h was only half that of 5. Ester 5 was also superior to 7 towards accumulation in the ovary. Based upon lipid extraction of these tissues and TLC analysis of the extracts, the lower affinity of the carbamate for steroid-secreting tissue does not seem

Table 2. Analysis of lipid-soluble radioactivity extracted from tissues

Tissue	% CHCl₃/CH₃OH extractable compound		% Parent compound as determined by TLC*	
	0.5 h	24 h	0.5 h	24 h
Cholesteryl benzoate (5)				
Adrenal cortex	93.2 ± 2.8	87.4 ± 1.8	81.4 ± 9.0	90.3 ± 6.4
	(85.1 ± 5.4)†	(93.6 ± 1.2)	(62.8 ± 19.2)	63.6 ± 5.8
Liver	92.4 ± 2.8	90.0 + 3.6	85.6 ± 1.2	81.2 + 24.4
	(64.3 ± 4.0)	(91.2 ± 2.2)	(76.2 ± 1.2)	(47.0 ± 14.4)
Plasma	87.8 ± 3.6	92.3 ± 4.8	91.9 ± 1.2	91.4 ± 2.3
	(48.5 ± 7.2)	(73.7 ± 10.8)	(66.4 ± 5.2)	(12.0 ± 7.6)
Cholesteryl carbamate (7)				
Adrenal cortex	92.4 ± 2.4	88.7 ± 1.4	64.7 ± 9.2	85.6 ± 4.8
	(56.8 ± 5.6)‡	(78.1 ± 3.4)	(83.2 ± 6.0)	(48.8 ± 40.4)
Liver	92.7 + 1.6	85.0 ± 2.4	74.8 ± 21.6	96.6 ± 6.0
	(40.5 ± 4.0)	(52.1 ± 5.8)	(74.2 ± 14.6)	(41.1 ± 26.4)
Plasma	82.1 ± 5.0	87.6 ± 3.2	90.3 ± 3.0	68.0 ± 9.4
	(7.8 ± 2.2)	(14.8 ± 8.4)	(63.5 ± 30.4)	(35.6 ± 27.4)

*Values represent the percent of total radioactivity ±SD comigrating with parent compound on chromatogram.
†‡Values in parentheses are the corresponding values obtained for pregnenolone-3-(2,6-demethyl-3-iodobenzoate) (6) and pregnenolone-3-(4-iodophenylcarbamate) (8) respectively.

to be explained by a greater susceptibility to *in vivo* hydrolysis (Table 2).

In marked contrast to the cholesterol derivatives, the benzoate and carbamate esters of pregnenolone (6 and 8) showed only slight affinity for steroid-secreting tissues. Furthermore these tissues displayed a rapid clearance of radioactivity by 24 h with a concomitant increase of radioactivity in the thyroid. This increase in thyroid radioactivity is believed to be related to deiodination following *in vivo* hydrolysis of these esters. Analysis of the adrenal, liver and plasma lipid extraction data (Table 2) provided further evidence as to the *in vivo* instability of the pregnenolone derivatives 6 and 8. For example in the case of the pregnenolone carbamate (8) TLC analysis of the adrenal, liver and plasma extracts at 24 h revealed that only 48.8, 41.1 and 35.6% of the radioactivy associated with these tissues was still present as the original compound. In contrast the corresponding values for the cholesteryl analog 7 at this time interval were 85.6, 96.6 and 68.0%, respectively.

In summary, despite the good accumulation of the radioiodinated cholesterol ester 5 in the adrenals, its concentration in this tissue at 24 h (26% of dose/g) does not differ significantly from 19-iodocholesterol (Van Dort *et al.*, 1984). Although more easily synthesized than the latter, 5 does not appear to offer any appreciable tissue localizing advantage over currently available radioiodinated cholesterols. A somewhat surprising observation was the lack of selectivity for adrenocortical tissue displayed by the pregnenolone esters examined in this study. This was in contrast to previous observations with a series of radioiodinated pregnenolone iodobenzoate esters which displayed high adrenal uptake (Van Dort *et al.*, 1984). In conclusion, future attempts to achieve selective adrenal uptake through chemical manipulation should take into account the substrate specificity of the sterol ester hydrolases, of which little is known at the present time.

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