Notes

Potential Tumor- or Organ-Imaging Agents. 23. Sterol Esters of Iopanoic Acid

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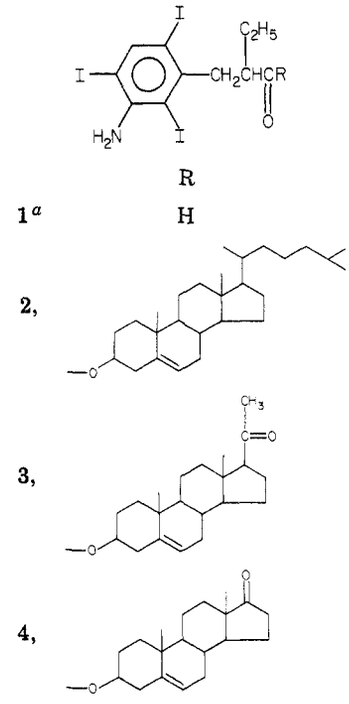
A series of sterol esters of iopanoic acid was synthesized and evaluated for their potential to selectively localize in liver and steroid-secreting tissues for possible application in either computed tomography or nuclear medicine imaging. Unlike free iopanoic acid (1), which was rapidly cleared following intravenous administration to rats, cholesteryl iopanoate (2) was found to accumulate in liver, adrenal cortex, and ovary. At 24 h, the ovary was found to contain the highest concentration of 2. The ability of 2 to accumulate in the above tissues was attributed to its resistance to hydrolysis. Pregnenolone iopanoate (3) and dehydroepiandrosterone iopanoate (4), on the other hand, were shown to reach unusually high concentrations in the adrenal cortex within 0.5 h of administration but declined to much lower levels by 24 h. Lipid extraction of tissues showed 3 and 4 to be susceptible to in vivo hydrolysis, which undoubtedly was a major factor in their clearance from adrenal tissue.

Over the past several decades significant advances have been made in the ability to visualize internal organs by noninvasive procedures. Two of the most widely used imaging modalities, radiography and radioisotope scanning, owe much of their success to the development of suitable radiopaques and radiopharmaceuticals. Interestingly, iodine plays an important role in both of these classes of diagnostic agents. On the one hand, it imparts the necessary electron density to radiopaques, while, on the other hand, its various isotopic states (e.g., ^{123}I and ^{131}I) emit the γ radiation essential for γ-camera scintigraphy.

A major pharmacological difference between radiopaques and radiopharmaceuticals is that large doses of the former are required for opacification of soft tissues, whereas the latter are administered in tracer doses. The recent advent of computed tomography (CT), however, now offers the possibility of reducing this dosage differential. In contrast to conventional X-ray imaging which reliably detects differences in tissue density of 5–10%, CT imaging can detect differences as small as 0.5%.[1] Accordingly, it is only a matter of time before new agents will be designed to capitalize on this increased sensitivity of CT. In this paper, we report the conversion of iopanoic acid (3-amino-α-ethyl-2,4,6-triiodobenzenepropanoic acid, 1), an established cholecystographic agent, to sterol esters in order to achieve selective localization in specific tissues.

Previous papers in this series described the marked propensity of iodinated acyl derivatives of cholesterol to localize in the adrenals and ovaries of the female rat.[2,3] The liver represented another site of accumulation for these agents. Many of these esters were found to resist in vivo hydrolysis and to appear in these tissues as the intact ester. These findings immediately raised the possibility that sterols might serve to selectively transport radiopaques, such as iopanoic acid, to steroid-secreting tissues and/or liver and that the major site of accumulation may depend on the nature of the sterol. To test this hypothesis, we selected cholesterol, pregnenolone, and dehydroepiandrosterone for our initial studies (Chart I), since these sterols all play an intermediary role in the adrenal and gonadal biosynthesis of steroid hormones.

Chart I. Sterol Esters of Iopanoic Acid



[a] Iopanoic acid.

Results and Discussion

The iopanoate ester of cholesterol (2) and dehydroepiandrosterone (4) could be obtained in good yields by allowing the sterols to react with the imidazolide of iopanoic acid in the presence of NaH, the method previously employed in the preparation of a large number of cholesterol esters.[2,3] However, the iopanoate ester of pregnenolone (3) could not be prepared by this method, presumably due to the well known ability of the pregnenolone side chain to epimerize under basic conditions.[4] Esterification of

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Table I. Distribution[a] of Radioactivity at 0.5 and 24 h after Intravenous Administration of Iopanoic Acid and Sterol Iopanoates to Female Rats[b]

	tissue	1[c]	2	3	4
0.5 h	adrenal cortex	0.373 ± 0.022	4.903 ± 0.718	23.083 ± 1.585	15.380 ± 0.920
	blood	1.205 ± 0.079	5.191 ± 0.441	1.727 ± 0.100	1.275 ± 0.123
	liver	1.461 ± 0.074	4.035 ± 0.543	5.214 ± 0.504	3.612 ± 0.259
	ovary	0.629 ± 0.048	5.161 ± 0.716	2.126 ± 0.203	1.886 ± 0.454
	thyroid	6.914 ± 0.569	0.868 ± 0.098	0.945 ± 0.068	1.392 ± 0.151
24 h	adrenal cortex	0.032 ± 0.006	11.029 ± 2.172	4.256 ± 0.736	3.958 ± 0.203
	blood	0.052 ± 0.007	0.696 ± 0.048	0.039 ± 0.003	0.085 ± 0.005
	liver	0.116 ± 0.010	6.587 ± 0.316	0.386 ± 0.024	0.108 ± 0.006
	ovary	0.042 ± 0.004	24.542 ± 2.964	1.085 ± 0.124	1.205 ± 0.170
	thyroid	265.14 ± 33.62	3.571 ± 0.218	156.70 ± 24.94	143.74 ± 21.58

[a] Expressed as percent administered dose per gram of tissue ± SEM. [b] $n = 5$ for all groups except compound 4 at 0.5 h, where $n = 4$. [c] Amount of compound administered per kilogram of body weight is as follows: 1, 0.28 mg; 2, 0.22 mg; 3, 0.27 mg; 4, 0.26 mg.

Table II. Analysis of Lipid-Soluble Radioactivity Extracted from Tissue Samples[a]

		% $CHCl_3/CH_3OH$ extractable compd		% parent compd as determined by TLC	
no.	tissue	0.5 h	24 h	0.5 h	24 h
1	adrenal cortex	48.4 ± 7.1	34.0 ± 3.7	82.3 ± 2.3	55.5 ± 7.2
	liver	34.2 ± 2.6	12.2 ± 2.7	98.2 ± 0.7	78.6 ± 5.6
	plasma	45.0 ± 1.3	18.7 ± 5.8	99.0 ± 0.2	57.5 ± 9.6
2	adrenal cortex	83.1 ± 1.7	92.1 ± 0.4	96.9 ± 0.3	96.9 ± 0.2
	liver	87.2 ± 2.0	91.2 ± 1.9	97.8 ± 0.7	97.8 ± 0.2
	plasma	83.4 ± 1.8	85.8 ± 1.2	96.0 ± 0.7	96.1 ± 0.2
3	adrenal cortex	89.5 ± 0.7	87.3 ± 0.4	92.1 ± 0.7	68.2 ± 1.7
	liver	87.6 ± 0.2	76.1 ± 1.1	89.2 ± 0.6	69.1 ± 2.2
	plasma	86.7 ± 1.0	60.0 ± 8.4	91.9 ± 0.3	44.6 ± 7.7
4	adrenal cortex	85.5 ± 2.0	85.8 ± 2.5	83.4 ± 0.7	16.8 ± 0.7[b]
	liver	86.0 ± 1.2	81.5 ± 0.6	61.8 ± 0.4	42.5 ± 1.1
	plasma	84.1 ± 0.3	63.1 ± 2.0	64.2 ± 2.1	38.0 ± 1.0

[a] Percent ± SEM. [b] Approximately 50% of lipid-extractable radioactivity from the adrenal cortex appeared as a slower-moving metabolite than administered ester.

pregnenolone, therefore, was accomplished under neutral conditions with dicyclohexylcarbodiimide (DCC) and the use of 4-(dimethylamino)pyridine (DMAP) as catalyst,[5] a method that afforded all three esters in excellent yield. To monitor tissue disposition, we labeled these esters and free iopanoic acid with radioiodine by isotope exchange with $Na^{125}I$ in a melt of acetamide.

Female Sprague–Dawley rats were employed to determine the ability of each of these agents to selectively localize in specific tissues. Each of the sterol esters was solubilized in normal saline with the aid of Tween-20, and the resulting solution was administered intravenously by tail vein. Groups of animals were sacrificed at 0.5 and 24 h, and the tissues were analyzed in a γ-counter. Although ten tissues were analyzed in this manner, only the results for those tissues displaying high concentrations of radioactivity are shown in Table I. The tissue distribution results for radioiodinated iopanoic acid (1) are shown for comparison.

Lipid extraction of plasma, adrenal, and liver was performed in order to obtain some insight as to the nature of radioactive products in these tissues. Table II summarizes the percent of lipid-extractable material present in these tissues at 0.5 and 24 h and indicates the amount still present in the form of parent compound.

The striking feature of the tissue distribution data is the marked change in the disposition of iopanoic acid upon esterification with various sterols. Moreover, the nature of the sterol has a major influence on the distribution. For example, cholesteryl iopanoate (2) localizes in the liver and steroid-secreting tissues, and the concentration in the latter is found to increase significantly with time. This is especially true for the ovaries, where the percent dose per gram of tissue reaches a value of approximately 25% at 24 h. Extraction of these tissues and TLC analysis also revealed that over 80% of the radioactivity was still in the form of cholesteryl iopanoate. Apparently, 2 is a poor substrate for cholesterol ester hydrolase (EC 3.1.1.13) present in liver and steroid-secreting tissues. The in vivo stability of 2 can also account for its diminished susceptibility to deiodination, as reflected by the low level of radioactivity appearing in the thyroid at 24 h [in contrast to [^{125}I]iopanoic acid (1), which gives rise to high levels of radioactivity in the thyroid at this time].

Polyacrylamide gel electrophoresis (PAGE) of plasma samples revealed that 75.2 and 66.7% of circulating 2 was associated with high-density lipoproteins (HDL) at 0.5 and 24 h, respectively. Since it has been shown that the adrenals and ovaries of rats acquire their cholesterol by an HDL receptor-mediated process,[6] the delivery of 2 to these tissues may occur by such a mechanism. The ability of 2 to remain and accumulate in these tissues can be explained by its stability to hydrolysis by tissue cholesterol ester hydrolase, as has been demonstrated previously for other radioiodinated cholesteryl esters.[7]

The pregnenolone and dehydroepiandrosterone esters (3 and 4) displayed a much different tissue distribution profile than either 1 or 2. Both 3 and 4 showed a marked propensity for adrenal cortical tissue. This was especially

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true for 3, which showed an unusually high value of 23% of administered dose per gram of tissue at 0.5 h. At this time, 40.7% of administered 3 was found associated with HDL. Since this is somewhat lower than that observed for 2, perhaps the high uptake in adrenal is not due entirely to a lipoprotein receptor-mediated process.

Tissue extraction data also showed 3 and 4 to be much less stable to hydrolysis and deiodination. As shown in Table II, only 60–65% of the radioactivity in plasma at 24 h after administration of 3 or 4 was lipid extractable, and less than 50% of this extractable radioactivity remained as the original ester. These results are indicative of hydrolysis of these esters to radioiodinated iopanoic acid and free sterol. This would account for not only the disappearance of tracer from the adrenal cortex but also the marked increase in thyroid radioactivity with time.

The rapid accumulation of 3 in adrenal cortex and its subsequent rapid clearance makes it an extremely interesting candidate for adrenal imaging. A major problem with the radiolabeled cholesterol analogues currently used for this purpose is that 4 or more days are required to clear the nonadrenal radioactivity in order to achieve adequate resolution of the adrenals.[8,9] This delays diagnosis and necessitates the use of long-lived nuclides, such as ^{131}I ($T_{1/2}$ = 8 days) or ^{75}Se ($T_{1/2}$ = 118.5 days). If the rapid adrenal uptake of 3 in rats extends to humans, it may be possible to employ the shorter-lived ^{123}I ($T_{1/2}$ = 13 h) as a tracer. Iodine-123 is not only a more suitable nuclide for imaging with γ-cameras, but its use would also significantly lower the radiation dose now associated with adrenal scintiscanning.[8]

The ability of these sterol esters to localize in liver and steroid-secreting tissues has prompted further studies with these agents in rabbits[10] and dogs.

Experimental Section

Melting points were determined on a Buchi melting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were obtained on a Varian EM360A spectrometer for solutions in $CDCl_3$ containing tetramethylsilane as internal reference. Infrared spectra (IR) of compounds in KBr pellets were obtained on a Perkin-Elmer 281 spectrophotometer. Elemental analyses were performed by Midwest Microlab, Ltd., Indianapolis, IN. All analyses were within ±0.4% of the calculated values. Thin-layer chromatography (TLC) was performed on Eastman polyethylene-backed silica gel plates with fluorescent indicator. Cholesterol, dicyclohexylcarbodiimide, and 4-(dimethylamino)-pyridine were obtained from the Aldrich Chemical Co., Milwaukee, WI. Dehydroepiandrosterone and pregnenolone were kindly furnished by G. D. Searle and Co., Skokie, IL. Iopanoic acid was a gift from Sterling-Winthrop Research Institute, Rensselaer, NY. Tween 20 was obtained from Sigma Chemical Co., St. Louis, MO. Rats were obtained from Spartan Research Animals, Inc., Haslett, MI.

Cholesteryl Iopanoate (2). A mixture of iopanoic acid (571 mg, 1.0 mmol) and cholesterol (387 mg, 1.0 mmol) in 5 mL of dichloromethane under nitrogen was treated with DCC (227 mg, 1.1 mmol) and DMAP (12 mg, 0.1 mmol) and stirred under nitrogen at room temperature overnight. The reaction mixture was diluted to 40 mL with dichloromethane and filtered from dicyclohexylurea, the filtrate was extracted twice with 40 mL of 0.5 N HCl, once with 40 mL of 10% $NaHCO_3$, and once with 40 mL of brine. The organic solution was dried ($MgSO_4$), and solvents were removed by rotary evaporation. The resulting oil was treated with a small amount of acetone and dried in vacuo to afford 890 mg (95%) of 2 as a pale yellow solid. Recrystallization from acetone afforded 2 as a white solid: mp 128–130 °C; NMR δ 8.14 (s, 1, *m*-H), 5.37 (m, 1, H-6), 4.85 (s, 2, NH_2), 4.80 (m, 1, H-3), 3.37 (d, 2, β-CH_2); IR (KBr) 3460, 3365, 2940, 1725 cm^{-1}. Anal. ($C_{38}H_{56}I_3NO_2$) C, H, I.

Pregnenolone iopanoate (3). Substitution of pregnenolone (317 mg, 1.0 mmol) for cholesterol in the above procedure afforded 808 mg (93%) of 3 as a pale yellow solid. Recrystallization from acetone afforded 3 as white needles: mp 196–197 °C; NMR δ 8.12 (s, 1, *m*-H), 5.40 (m, 1, H-6), 4.85 (s, 2, NH_2), 4.73 (m, 1, H-3), 3.35 (d, 2, β-CH_2), 2.11 (s, 3, 21-CH_3); IR (KBr) 3480, 3382, 2963, 2930, 1725, 1687 cm^{-1}. Anal. ($C_{32}H_{42}I_3NO_3$) C, H, I, N.

Dehydroepiandrosterone Iopanoate (4). Substitution of dehydroepiandrosterone (288 mg, 1.0 mmol) for cholesterol afforded 824 mg (98%) of 4 as a pale yellow solid. Recrystallization from acetone afforded 4 as white needles: mp 194–194.5 °C; NMR δ 8.08 (s, 1, *m*-H), 5.40 (m, 1, H-6), 4.78 (s, 2, NH_2), 4.70 (m, 1, H-3), 3.32 (d, 2, β-CH_2); IR (KBr) 3360, 3460, 2940, 1742, 1732 cm^{-1}. Anal. ($C_{30}H_{38}I_3NO_3$) C, H, I.

Isotope Exchange in Acetamide Melt. The isotope exchange with $Na^{125}I$ in acetamide was performed as previously reported,[2,3] except for the workup of [^{125}]2, which involved preparative thick-layer chromatography (0.25 mm Merck silica gel plate with fluorescent indicator, dichloromethane as eluent). Radiochemical purity was established by TLC with unlabeled ester as the standard. Reaction times, temperatures, and yields for each compound were as follows.

[^{125}I]1: 6 h at 140 °C; radiochemical yield 14%; specific activity 155.6 μCi/mg; R_f (acetone/HOAc, 99:1) 0.28, R_f (ethyl acetate/MeOH/HOAc, 80:20:1) 0.33.

[^{125}I]2: 4 h at 165 °C; radiochemical yield 35%; specific activity 1666 μCi/mg; R_f (benzene) 0.50, R_f (CCl_4) 0.08.

[^{125}I]3: 2 h at 195 °C; radiochemical yield 25%; specific activity 350 μCi/mg; R_f (diethyl ether) 0.68, R_f (dichloromethane) 0.29.

[^{125}I]4: 4.5 h at 175 °C; radiochemical yield 53%; specific activity 358 μCi/mg; R_f (chloroform) 0.53, R_f (ethyl acetate) 0.67.

Tissue Distribution Studies. The radiolabeled compounds were dissolved in benzene, and Tween 20 was 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) resulted. The radiolabeled compound, thus solubilized, was administered intravenously to adult female Sprague-Dawley rats weighing 200-250 g. Four to five rats were used for each compound at each time period, and the dose ranged between 5 and 30 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. Adrenal cortex was carefully dissected away from the medulla. Weighed samples of tissue were placed in cellulose acetate capsules and counted (84% efficiency) in a well scintillation counter (Searle 1185). The concentration of radioactivity in each tissue was expressed as the percentage of administered dose per gram of tissue, which was calculated as follows:

$$\frac{(\text{CPM} - \text{BKG})/\text{mg of tissue} \times 1000 \times 100}{\text{efficiency} \times 2.2 \times 10^6\ \text{dpm}/\mu\text{Ci} \times \mu\text{Ci dose}}$$

The results are summarized in Table I.

Plasma and Tissue Extractions. Radioactivity was extracted from plasma by the procedure described previously.[3] Adrenal cortex and liver samples were homogenized, extracted, and analyzed by TLC as described previously.[11] For TLC analysis of the lipid extracts for cholesterol iopanoate (2), a system of petroleum ether/diethyl ether (7:2) was employed, whereas for 3 and 4, a system of benzene/ethyl acetate (9:1) served as eluent. 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. The results obtained for

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plasma are summarized in Table II.

Plasma Electrophoresis. Polyacrylamide gel electrophoresis of plasma samples was performed according to the method of Narayan et al.[12] as previously described.[13] The amount of radioactivity associated with each lipoprotein class was determined by sectioning the gels and counting each section in a γ-counter. The radioactivity associated with each lipoprotein band was expressed as a percentage of the total radioactivity applied to the gel.

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Preliminary Studies of Mesoionic 3-(Substituted-aryl)-ψ-oxatriazoles as Potential Antihypertensive Agents

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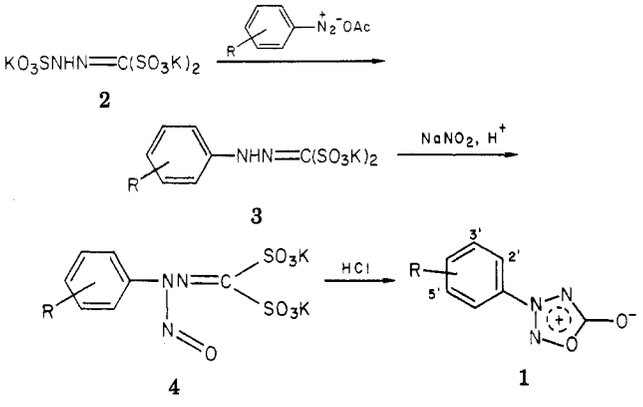
Several mesoionic 3-(substituted-aryl)-ψ-oxatriazole derivatives were prepared and evaluated as potential antihypertensive agents. 3-(4-Methylphenyl)-ψ-oxatriazole was found to produce a significant hypotensive effect in rats, which was characterized by a rapid (2–3 min) onset of action. Maximal effects were achieved within 30 min, and a substantial decrease in mean arterial blood pressure was recorded even 5 h after administration.

Mesionic compounds, as a class, have received considerable attention from a chemical and/or physicochemical standpoint; however, their pharmacological potential, for the most part, remains relatively unexplored. Several years ago, it was discovered that 3-alkyl derivatives of the mesoionic ψ-oxatriazole (i.e., oxatriazolium-5-olate, 1) possess a moderate degree of hypotensive activity characterized by a rapid onset and a long duration of action as measured in the anesthetized dog.[1,2] The results of these studies were supported and extended by Thomas and co-workers.[3] Because optimal activity appears to be associated with the increased lipophilic nature of the 3-alkyl substituent (e.g., *t*-Bu > Et > Me), it was of interest to explore several 3-aryl derivatives. We now report the synthesis and the results of a preliminary evaluation of a series of 3-aryl-ψ-oxatriazoles as potential hypotensive agents.

Chemistry. The synthesis of the mesoionic compounds is shown in Scheme I. Tripotassium sulfohydrazonomethanedisulfonate (**2**) was prepared in four steps according to the method of von Pechmann and Manck.[4] Compound **2** was allowed to react with the diazonium acetates of the appropriately substituted anilines to yield the corresponding arylhydrazonomethanedisulfonate salts, **3**, which were further nitrosated to afford **4**. The nitroso derivatives **4** were not isolated and characterized but were cyclized by stirring in acid at room temperature to afford the desired mesoionic products **1**. All mesoionic products displayed a negative Liebermann nitroso test.

Scheme I



Results and Discussion

Compounds **1a–d** were initially prepared and evaluated; the 3-(4-methylphenyl) derivative **1b** was studied in greater detail than the other compounds. When administered to rats, **1b**, in doses of 1–90 mg/kg, produced a dramatic dose-dependent decrease in blood pressure; maximal effects were achieved in less than 1 h, and Table II shows the effects of several doses of **1b** recorded during the first hour after administration. Doses of **1b** greater than 10 mg/kg produced a decrease in blood pressure that was of long duration (i.e., after 5 h, blood pressure was still at least 20% below control values), and percent decreases in both systolic and diastolic pressures were essentially equal (data not shown). A typical time course for **1b** (at 15 mg/kg) is shown in Figure 1.

Because the maximal effect of 10 mg/kg of **1b** occurred within 30 min, this dose and time parameter were chosen for single dose studies of the unsubstituted, 4-chloro-, and 3,4-dichlorophenyl derivatives (**1a**, **1c**, and **1d**, respectively) in order to make comparisons with **1b**. Table III shows

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