their membrane receptors[54] may provide rational targets for inhibitor design. With the recent advances in membrane technology, the molecular interaction of NSAIDS with model membrane systems can readily be studied by NMR, ESR, membrane potential, and other physical measurements.[55,56] It may be noted that in QSAR analysis only the physical properties of drug molecules themselves have been generally measured and evaluated. Such membrane information may provide a set of physicochemical parameters to denote actions on drug targets and to augment our QSAR analysis of new membrane regulators. With this new knowledge and new concepts, we are optimistic that more selective and superior NSAIDS and SAARDS will continually evolve in the next 2 decades to alleviate the sufferings of arthritic patients.

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Finally, an association of various arthritis disorders with the genetic HLA determinants of patients, e.g., rheumatoid arthritis and ankylosing spondylitis with HLA antigens DW4 and B27, respectively, has been observed recently. These associations may be related to the influence of genetic determinants on specific immunological events, such as antigen processing and the interactions between macrophage and T lymphocytes. In this light, one may hope that progress in immunogenetics and selective immunoregulation in the near future would bring forth better understanding of pathogenic mechanisms, early diagnosis of susceptible patients, and open the possibility of selective and preventive medicine for this family of degenerative and debilitating diseases. We are deeply appreciative to Dr. Burger's dedicated educational and research effort in medicinal chemistry in the past 50 years. Looking ahead, medicinal chemical research may further advance in the coming half century through chemotherapy to preventive medicine, from enzyme inhibition to phenotypic regulation. Selective antiarthritic therapy based on immunogenetics may constitute such an opportunity.

Communications to the Editor

Potential Organ- or Tumor-Imaging Agents. 21. Acyl-Labeled Esters of Cholesterol[1]

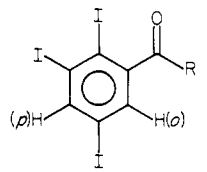
Sir:

Radioiodinated derivatives of cholesterol[2-4] have been widely used as imaging agents for the diagnosis of a variety of adrenal disorders in humans.[5] More recently, esters of radioiodinated cholesterol have also been shown to selectively accumulate in adrenals as well as ovaries.[6,7] In these, as well as other studies to date, it has been assumed that the appropriate γ-emitting radionuclide (^{131}I, ^{75}Se,[8] ^{123m}Te[9]) must form a part of the cholesterol molecule, either by direct attachment to the steroid nucleus or by incorporation into the side chain, in order to achieve target-organ specificity.

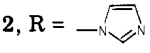
This communication was prompted by our observation that cholesteryl oleate radiolabeled in the potentially hydrolyzable acyl moiety accumulated in target tissues at 0.5 h with approximately the same degree of selectivity noted for cholesteryl oleate radiolabeled in the steroid nucleus (Table I). As a consequence of this finding, the synthesis of cholesteryl esters bearing radioiodine on the acyl moiety was undertaken. We report here the synthesis and tissue distribution for one of these radiolabeled esters, cholesteryl 2,3,5-tri[^{125}I]iodobenzoate (**3**).

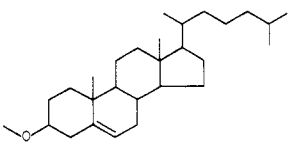
Table I. Distribution of Radioactivity at 0.5 h After Intravenous Administration of Radiolabeled [^{14}C]Cholesteryl Oleate to Rats

	% administered dose/g of tissue ± SEM	
tissue	4-^{14}C (n = 3)	oleate 1-^{14}C (n = 4)
adrenal cortex	3.852 ± 0.084	2.448 ± 0.128
blood	5.781 ± 0.276	5.196 ± 0.097
liver	1.569 ± 0.261	1.236 ± 0.141
ovary	2.815 ± 0.388	2.088 ± 0.158
thyroid	0.446 ± 0.036	0.344 ± 0.017



1, R = -OH

2, R = 

3, R = 

Cholesteryl 2,3,5-triiodobenzoate (**3**) was prepared from 2,3,5-triiodobenzoic acid (**1**) in dry THF by means of the imidazolide (**2**):[10] yield 65%; mp 199-200.5 °C; TLC R_f

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Table II. Distribution of Radioactivity After Intravenous Administration of Radioiodinated Cholesterol Derivatives to Rats

	% administered dose/g of tissue ± SEM			
	0.5 h		24 h	
tissue	19-[^{125}I]iodocholesterol (n = 5)	cholesteryl 2,3,5-tri[^{125}I]iodobenzoate (n = 5)	19-[^{125}I]iodocholesterol (n = 5)	cholesteryl 2,3,5-tri[^{125}I]iodobenzoate (n = 4)
adrenal cortex	14.162 ± 2.015	5.455 ± 0.478	26.486 ± 0.701	9.032 ± 1.846
blood	1.746 ± 0.179	5.460 ± 0.232	0.353 ± 0.012	0.568 ± 0.064
liver	4.662 ± 0.476	2.726 ± 0.049	0.616 ± 0.027	5.106 ± 0.218
lung	1.564 ± 0.181	1.490 ± 0.117	0.849 ± 0.045	0.703 ± 0.038
ovary	4.397 ± 0.438	6.148 ± 1.082	10.725 ± 0.506	16.190 ± 0.784
spleen	2.131 ± 0.321	0.570 ± 0.039	0.834 ± 0.028	1.680 ± 0.094
thyroid	3.586 ± 0.676	0.470 ± 0.059	251.522 ± 27.116	2.630 ± 0.470

(silica gel; benzene, CCl_4) 0.57, 0.40; NMR ($CDCl_3$) δ 4.85 (m, C-3α H), 5.45 (m, C-6 vinyl H), 7.73 (d, $J_{o,p}$ = 3 Hz, p-H), 8.32 (d, o-H); IR (KBr) 1726, 1701 (approximately equal) ($CHCl_3$), 1723. Anal. ($C_{34}H_{47}I_3O_2$) C, H, I.

Radiolabeled **3** was obtained by isotope exchange of 2,3,5-triiodobenzoic acid (**1**) with Na^{125}I in glacial HOAc at reflux for 1 h. The radiolabeled acid was precipitated by the addition of H_2O and isolated by centrifugation. The product was taken up in benzene and dried by azeotropic distillation, and the solvent was removed. The residue was dissolved in dry THF and esterified as described above, to give cholesteryl 2,3,5-tri[^{125}I]iodobenzoate: radiochemical yield 50%. It showed a single radioactive peak coincident with unlabeled ester on TLC.

Tissue distribution studies were performed in adult female Sprague–Dawley rats. Rats received intravenous injections of either ^{14}C-labeled cholesteryl oleate (4.0–4.3 μCi, 0.08 μmol, New England Nuclear), 19-[^{125}I]iodocholesterol (22.0 μCi, 0.05 μmol, prepared as previously described[2]), or cholesteryl 2,3,5-tri[^{125}I]iodobenzoate (**3**; 3.8–7.6 μCi, 0.16–0.28 μmol) and were killed at 0.5 or 24 h after injection. Samples of tissues were removed and analyzed for radioactivity as previously described.[11]

At 0.5 h, cholesteryl 2,3,5-tri[^{125}I]iodobenzoate (**3**) showed significantly higher levels of radioactivity in the adrenals and ovaries than [^{14}C]cholesteryl oleate (Tables I and II). **3** showed less accumulation in the adrenals than 19-iodocholesterol at both 0.5 and 24 h, but it gave higher levels of radioactivity in the ovaries, particularly at 24 h (Table II). The amount of radioactivity in the thyroid indicates that the aromatic iodo compound (**3**) is notably more stable to in vivo deiodination than 19-iodocholesterol. From the point of view of radioscanning of the adrenals or ovaries, a shortcoming of **3** is the high concentration of radioactivity appearing in the liver.

Nevertheless, these results suggest that radiolabeling the acyl portion of steroid esters may be a useful approach for imaging agents. In addition, polyiodinated compounds, like **3**, may also have potential as contrast-enhancing agents for computerized axial tomography procedures. Both of these possibilities are being pursued through the synthesis of other compounds whereby we hope to separate the adrenal and ovarian accumulation and reduce the liver uptake.

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