SYNTHESIS OF NEW RADIOIODINATED BARBITURATES AS POTENTIAL BRAIN IMAGING AGENTS

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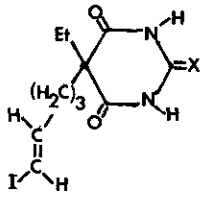
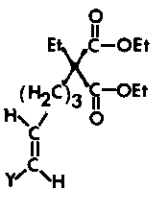
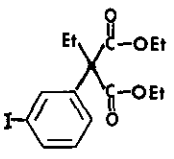
A new barbituric acid analog, (E)-5-ethyl-5-(1-iodo-1-penten-5-yl)barbituric acid (1) was prepared and labeled with iodine-125 at the vinyl iodide (E-1) position. The radiolabeled analog 1 showed high brain uptake in rats, but also showed significant in vivo deiodination (J. Med. Chem., in press). Attempts to stabilize iodine toward in vivo deiodination by structurally modifying the functional groups on the pyrimidine ring and by attaching the radioiodine to a phenyl ring have been pursued. Two new ^{125}I-labeled barbituric acid analogs, (E)-5-ethyl-5-(1-iodo-1-penten-5-yl)-2-thiobarbituric acid (4) and 5-ethyl-5-(meta-iodophenyl)-barbituric acid (6) have now been prepared. Iodination of diethyl (E)-2-ethyl-2-(1-borono-1-penten-5-yl) malonate (2) with sodium iodide in the presence of chloramine T follwed by ring annulation of the iodinated intermediate, diethyl (E)-2-ethyl-2-(1-iodo-1-penten-5-yl)malonate (3) with thiourea in the presence of sodium ethoxide, gave the (E)-5-ethyl-5-(1-iodo-1-penten-5-yl)-2-thiobarbituric acid (4). Diethyl 2-ethyl-2-phenyl malonate was treated with thallium(III)trifluoroacetate followed by addition of aqueous potassium iodide to provide diethyl 2-ethyl-2-(meta-iodophenyl)malonate (5). The malonic ester derivative was condensed with urea in the presence of sodium hydride to give the desired 5-ethyl-5-(meta-iodophenyl)-barbituric acid (6) and a decarbethoxylation product, 2-(meta-iodophenyl)butyric acid. Iodine-125-labeled 4 and 6 were synthesized in the same manner and the tissue distribution of these new agents evaluated in rats. Both [^{125}I] 4 and [^{125}I] 6 showed high brain uptake. Significant in vivo deiodination was detected with [^{125}I] 4 whereas [^{125}I] 6 was found to be stable to in vivo deiodination. Details of the syntheses and structure-biodistribution relationships of these new barbiturates will be discussed.



1, X = O
4, X = S



2, Y = H_2BO_2
3, Y = I



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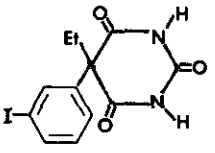

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