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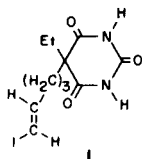
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Two new ^{125}I -labeled barbituric acid analogs, 5-ethyl-5-(*E*-1-iodo-1-penten-5-yl)-2-thiobarbituric acid (**4**) and 5-ethyl-5-(*m*-iodophenyl)barbituric acid (**7**), have been prepared and evaluated in rats as potential cerebral perfusion agents. Annulation of 2-ethyl-2-(*E*-1-iodo-1-penten-5-yl)malonate (**3**) with thiourea in the presence of sodium ethoxide gave the 5-ethyl-5-(*E*-1-iodo-1-penten-5-yl)-2-thiobarbituric acid (**4**). Diethyl 2-ethyl-2-phenylmalonate was treated with thallium(III) trifluoroacetate followed by addition of aqueous potassium iodide to provide diethyl 2-ethyl-2-(*m*-iodophenyl)malonate (**10**). The malonic ester derivative **10** was condensed with urea in the presence of sodium hydride to give the desired 5-ethyl-5-(*m*-iodophenyl)barbituric acid (**7**), and a decarbethoxylation product, 2-(*m*-iodophenyl)butyric acid (**11**). Iodine-125-labeled **4** and **7** were synthesized in the same manner and the tissue distribution of these new agents evaluated in rats. Both [^{125}I] **4** and [^{125}I] **7** showed high brain uptake. Significant *in vivo* deiodination was detected with [^{125}I] **4** whereas [^{125}I] **7** was found to be stable to deiodination.

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Barbituric acid analogs are widely used as sedative and hypnotic agents [1]. These agents are highly lyophilic and freely cross the intact blood brain barrier [2]. New methods have recently been developed to radiolabel barbituric acid analogs with suitable long-lived gamma-emitting radionuclides [3,4]. Such radiolabeled agents could potentially be used to monitor regional perfusion parameters and assess changes in cerebral blood flow. In a recent study we reported the synthesis of a unique iodovinylbarbituric acid analog, 5-ethyl-5-(*E*-1-iodo-1-penten-5-yl)barbituric acid (**1**) [4]. In rats compound **1** exhibited a brain:

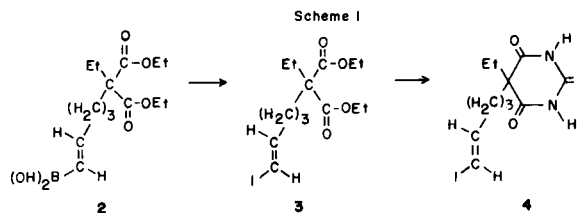


blood ratio of ~ 1 within 2-5 minutes after intravenous administration, followed by a rapid washout of radioactivity from the brain. Although the iodovinylbarbituric acid analog **1** appeared stable to facile chemical deiodination, this agent suffered extensive *in vivo* deiodination with consequent accumulation of iodide in the thyroid. As a continuation of this program, our studies have now been directed toward the synthesis of iodinated barbituric acid analogs with increased lipophilicity and stability to *in vivo* deiodination. The synthesis and tissue distribution studies of the 2-thio and 5-iodophenyl analogs of **1** are described in this report.

Chemistry.

Our synthesis of diethyl 2-ethyl-2-(*E*-1-iodo-1-penten-5-yl)malonate (**3**) *via* iodination of diethyl 2-ethyl-2-(*E*-1-penten-1-boronic acid-5-yl)malonate (**2**) with sodium iodide in the presence of chloramine-T has been described previ-

ously [4]. Condensation of **3** with thiourea in the presence of sodium ethoxide (NaOEt) in absolute ethanol (EtOH) provided 5-ethyl-5-(*E*-1-iodo-1-penten-5-yl)-2-thiobarbituric acid (**4**) which was purified by silica gel column chromatography. The formation of 6-ethoxycarbonyl-*E*-1-iodo-1-octen-6-carboxylic acid [4], an obvious hydrolytic product of **3** observed during the synthesis of **1**, was not detected in this reaction. The absence of this hydrolytic product could be attributed to the greater reactivity of **3** with thiourea compared with urea. Thiobarbituric acid **4** was identified on the basis of proton nuclear magnetic resonance spectroscopy (nmr) in which the signals for vinyl and alkyl protons appeared at the expected positions identical to those observed for the same protons of 5-ethyl-5-(*E*-1-iodo-1-penten-5-yl)barbituric acid (**1**) [4]. The signal for NH protons of **4** appeared at 10.25 ppm (δ) and was deshielded by ~ 1.15 ppm as compared to that of the corresponding oxo



analog **1**. The elemental analysis of **4** was consistent with its structure. The iodine-125-labeled thiobarbituric acid **4** was prepared by ring closure of [^{125}I] **3**, which was synthesized from **2** using Na^{125}I and chloramine-T as described earlier. Both **1** and thiobarbituric acid **4** appear to be stable to normal exposure to temperature, light and moisture. However, to our surprise, these compounds suffered rapid *in vivo* deiodination [4]. This phenomenon is described in the biological evaluation section of this paper. In view of the significant brain uptake exhibited by

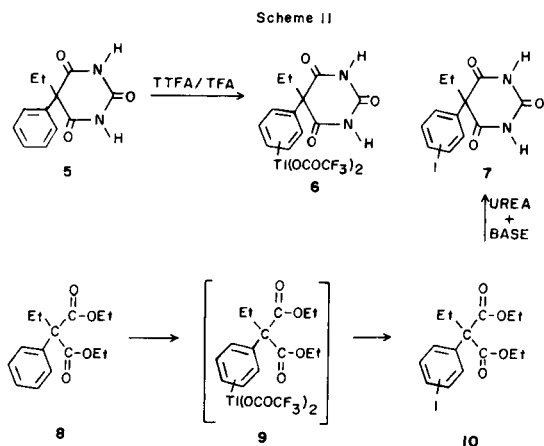
1 and **4**, we were prompted to extend our studies to evaluate an iodophenylbarbituric acid analog which would be expected to be resistant to *in vivo* deiodination.

Aromatic thallation with thallium(III)trifluoroacetate [5] (TTFA) under thermodynamically controlled conditions followed by addition of aqueous potassium iodide represents a facile method for the synthesis of aromatic iodides

derivative by this route were unsuccessful and resulted only in the recovery of unchanged starting material even after heating **5** with TTFA/TFA at 73° for 48 hours. The NH and tautomeric OH groups of **5** are capable of complexing with TTFA and may on prolonged heating lead to gradual decomposition of TTFA with regeneration of the nonthallated substrate [6].

Following an alternative approach, diethyl 2-ethyl-2-phenylmalonate (**8**) [7], was heated at 72 ± 1° with TTFA/TFA for 64 hours followed by treatment with aqueous potassium iodide to give diethyl 2-ethyl-2-(iodophenyl)malonate (**10**). Based upon the nmr analysis, the iodine appeared to be in the *meta* position of the phenyl ring. The substituted malonate **8** was prepared by alkylation [8] of diethyl 2-phenylmalonate with ethyl bromide. Under thermodynamically controlled conditions (72°), *meta* thallation [6] would be expected and thus lead to the *m*-iodophenyl product. Steric considerations precluded the possibility of an electrophilic thallation at the *ortho* position of the phenyl ring of **8**, similar to that observed in α,α -dimethylphenylacetic acid [6]. Further, the signals for the phenyl protons of **10** in the nmr spectrum were consistent with *meta* substitution. In addition, the absence of a two-doublet pattern (AA'BB') for the phenyl protons in the nmr spectrum of **10** indicated that *para* substitution did not occur.

Compound **10** was annulated with urea in the presence of sodium ethoxide in ethanol. Purification by silica gel column chromatography gave 5-ethyl-5-(*m*-iodophenyl)



of predominantly *m*-orientation [6]. Thus, direct treatment of 5-ethyl-5-phenylbarbituric acid (**5**) with TTFA in trifluoroacetic acid (TFA) followed by treatment with aqueous potassium iodide would be expected to provide 5-ethyl-5-(iodophenyl)barbituric acid (**7**) via the corresponding bis(trifluoroacetyl)thallium(III) phenyl derivative **6**. However, our attempts to obtain the iodophenylbarbituric acid

Table 1

Distribution of Radioactivity in Tissues of Fischer 344 Female Rats Following *i.v.* Administration of Radioiodinated Barbituric Acid Analogs (a)

Compound	Time after injection	Mean percent injected dose/gram (range)						Brain: Blood (Mean)
		Brain	Blood	Thyroid	Liver	Fat	Muscle	
^{[125]I} 4	2 minutes	0.59 (0.46-0.69)	0.99 (0.97-1.1)	9.81 (8.07-10.57)	5.08 (4.32-5.91)	0.19 (0.14-0.20)	0.35 (0.29-0.43)	0.59
	5 minutes	0.49 (0.42-0.58)	0.75 (0.66-0.90)	9.22 (6.95-11.23)	3.90 (3.48-4.18)	0.47 (0.33-0.97)	0.32 (0.25-0.41)	0.68
	30 minutes	0.22 (0.17-0.26)	0.65 (0.59-0.75)	18.31 (14.89-21.95)	1.74 (1.40-1.97)	1.97 (1.71-2.28)	0.20 (0.16-0.27)	0.34
	1 hour	0.17 (0.14-0.19)	0.62 (0.60-0.64)	42.72 (37.41-47.79)	1.73 (1.61-1.84)	2.14 (1.94-2.29)	0.18 (0.16-0.19)	0.28
	4 hours	0.09 (0.07-0.10)	0.48 (0.38-0.57)	211.62 (196.82-237.28)	1.03 (0.82-1.23)	0.92 (0.97-0.98)	0.11 (0.09-0.13)	0.19
	24 hours	0.008 (0.008-0.008)	0.04 (0.04-0.04)	330.74 (238.18-408.71)	0.05 (0.04-0.06)	0.03 (0.02-0.05)	0.01 (0.01-0.01)	0.24
^{[125]I} 7	5 minutes	0.46 (0.42-0.47)	0.82 (0.70-0.92)	5.89 (5.42-6.34)	1.92 (1.78-2.11)	0.23 (0.19-0.31)	0.46 (0.36-0.48)	0.57
	30 minutes	0.52 (0.37-0.60)	0.80 (0.64-0.87)	5.96 (5.69-6.30)	1.74 (1.33-1.84)	0.90 (0.79-1.04)	0.43 (0.36-0.46)	0.64
	1 hour	0.51 (0.49-0.57)	0.79 (0.76-0.82)	6.82 (5.19-8.3)	1.80 (1.78-1.90)	0.93 (0.82-1.02)	0.48 (0.43-0.55)	0.65
	4 hours	0.43 (0.41-0.46)	0.73 (0.69-0.75)	6.24 (5.14-7.2)	1.65 (1.52-1.83)	0.69 (0.66-0.71)	0.37 (0.35-0.38)	0.59

(a) Four rats were used for each time period; [¹²⁵I] **4** (sp. act. 215 mCi/mmmole, dose: 5.57 μ Ci/animal) and [¹²⁵I] **7** (sp. act. 34.3 mCi/mmmole, dose: 5.53 μ Ci/animal) in phosphate buffer (pH 7.4) were administered by injection in a lateral tail vein.

yl)barbituric acid (**7**) and a by-product identified as 2-(*m*-iodophenyl)butyric acid (**11**). The by-product was apparently formed by hydrolysis followed by decarboxylation, or decarbethoxylation [9], of **10**. The nmr, mass spectral and elemental analyses obtained for **7** and **11** were consistent with the assigned structures. Radioiodinated **7** was similarly prepared from [¹²⁵I]-**10** which was synthesized from **8** using K¹²⁵I.

Biological Evaluation.

The tissue distribution of the radioiodinated compounds, 5-ethyl-5-(*E*-1-[¹²⁵I]iodo-1-penten-5-yl)-2-thiobarbituric acid ([¹²⁵I]-**4**) and 5-ethyl-5-(*m*-[¹²⁵I]phenyl)barbituric acid ([¹²⁵I]-**7**), was evaluated in female Fischer 344 rats and the data are reported in Table 1. Four animals per time period were used and the distribution of radioactivity in brain, blood, thyroid, liver, fat and muscle was determined after intravenous administration of the radioiodinated agents. The radioiodinated thiobarbituric acid analog **4** was evaluated for the time periods ranging from 2 minutes to 1 day and showed significant brain uptake within 2-5 minutes after administration. The data from Table 1 indicate that this agent suffered *in vivo* deiodination, with gradual accumulation of radioiodide in the thyroid. In this respect, the brain uptake and *in vivo* deiodination patterns of [¹²⁵I]-**4** were similar to the data reported earlier for [¹²⁵I]-**4** [4].

The radioiodinated phenylbarbituric acid analog **7** was evaluated similarly for time periods ranging from 5 minutes to 4 hours. Iodine-125-labeled **7** exhibited brain uptake similar to that observed with [¹²⁵I]-**4**, but the radioiodinated thiobarbituric acid showed longer brain retention. Compound [¹²⁵I]-**7** exhibited a brain:blood ratio of ~0.6 after 4 hours, nearly three times greater than that found for [¹²⁵I]-**4**. The data from these experiments suggest that the aromatic (phenyl) iodide **7** is more stable to *in vivo* deiodination, as measured by accumulation of radioiodide in the thyroid, than the vinyl iodides **1** or **4**. These data also further demonstrate that the barbituric acid analogs freely cross the intact blood:brain barrier and that these agents are good candidates for further investigations.

EXPERIMENTAL

The melting points were determined in capillary tubes using a Büchi SP apparatus and are uncorrected. The low-resolution mass spectra (ms) were recorded at 70 eV using a Kratos MS 25 instrument. The proton nuclear magnetic resonance spectra (nmr) were obtained at 60 MHz with a Varian 360-L instrument. Samples (30-40 mg) were dissolved in the solvents indicated and the resonances are reported downfield (δ) from the internal tetramethylsilane standard. The presence of exchangeable protons was confirmed by treatment with deuterium oxide followed by reintegration of the nmr spectrum. Thin-layer chromatographic analyses (tlc) were performed using 250 μ m thick layers of silica gel G PF-254 coated on glass plates (Analtech, Inc.). Spots on the TLC plates were detected by

observation under short wave uv light or exposure to iodine vapor. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee.

Materials.

Absolute ethanol was stored over 4 Å molecular sieves several days before use. All other chemicals and solvents were analytical grade and were used without further purification. The sodium [¹²⁵I]iodide was purchased from New England Nuclear, Inc. (North Billerica, MA). Diethyl phenylmalonate and thallium(III)trifluoroacetate (TTFA) were purchased from Aldrich Chemical Co. (Milwaukee, Wisconsin). Sigma grade silica gel (SIL-A-200, 60-200 mesh) was used for the column chromatography.

Animal Tissue Distribution Experiments.

The radioiodinated compounds were evaluated using 10-12 week old female Fischer 344 rats (141-191 g). The animals were allowed food and water *ad libitum* prior to and during the course of the experiment. The radioiodinated agents were formulated in pH 7.4 phosphate buffer. The solution was filtered through a 0.22 μ m Millipore and 0.5 ml of the solution was injected *via* a lateral tail vein into the ether-anesthetized animals. At the desired time interval after injection, the animals were anesthetized with ether and sacrificed by cervical fracture. The organs were excised, rinsed with saline solution, blotted dry and placed in tared vials and weighed. The radioactivity was determined in a Packard auto-gamma counter and the percent injected dose per gram of tissue was calculated.

5-Ethyl-5-(*E*-1-iodo-1-penten-5-yl)-2-thiobarbituric Acid (**4**).

Thiourea (1.14 g, 15 mmoles) was added to a solution of sodium hydride (60% oil dispersion, 360 mg, 9 mmoles) in absolute ethanol (12 ml) and dissolved by stirring and warming. Diethyl 2-ethyl-2-(*E*-1-iodo-1-penten-5-yl)malonate (**3**) (1.2 g, 3 mmoles), was then added to the thiourea solution. The intermediate **3** was obtained by coupling of *E*-5-iodo-1-penten-1-ylboronic acid with diethyl 2-ethyl-2-sodiummalonate followed by iodination with sodium iodide and chloramine-T in the usual manner [4]. The resulting solution was refluxed (bath temperature, ~95°) for 18 hours under anhydrous conditions. The solvent was evaporated under reduced pressure to a residue which was dissolved in water and adjusted to pH 11 with 1 *N* aqueous sodium hydroxide. The aqueous basic portion was extracted well with ethyl ether (ether) which was discarded. The aqueous portion was then acidified to pH 2 with 1 *N* aqueous hydrochloric acid and extracted with ether (2 $\times$ 25 ml). The combined ether portion was washed with water (25 ml) and dried with sodium sulfate. The ether portion was evaporated under vacuum to provide a residue which was passed through a column (2.5 $\times$ 30 cm) packed with silica gel slurry (75 ml) in chloroform. Elution of the column with chloroform provided a homogenous product which was crystallized from benzene and petroleum ether to yield 440 mg (40%) of **4** as light yellow crystals, mp 89-91° (softens at 84-86°); nmr (deuteriochloroform): δ 10.27 [s (br), 2, NH and NH], 5.9-6.7 (m, 2, I—CH=CH), 1.1-2.35 (m, and m, 2 and 6, CH₂ of ethyl and pentenylmethylenes), 0.92 (t, 3, CH₃ of ethyl); ms: *m/e* 366 (M⁺).

Anal. Calcd. for C₁₁H₁₅IN₂O₂S: C, 36.07; H, 4.13; N, 7.65; S, 8.76; I, 34.65. Found: C, 36.29; H, 4.26; N, 7.46; S, 8.81; I, 34.41.

Diethyl 2-Ethyl-2-(*m*-iodophenyl)malonate (**10**).

The precursor, diethyl 2-ethyl-2-phenylmalonate (**8**), was prepared [10] by treating diethyl 2-phenylmalonate with sodium hydride followed by addition of ethyl bromide and purification of product **8** by distillation under vacuum. Precursors **8** (396 mg, 1.5 mmoles) was added to a solution of TTFA (1.0 g, 1.8 mmoles) in TFA (2.0 ml) shielded from light. The reaction solution was stirred in the dark at 72 $\pm$ 1° for 64 hours and then cooled to room temperature. A solution of potassium iodide (1.7 g, 10.5 mmoles) in water (5 ml) was added to the vigorously stirred reaction solution. The stirring was continued for 1 hour and ether (25 ml) and water (25 ml) were added and the mixture partitioned. The ether layer was separated and successively washed with aqueous solutions of 10% sodium bicarbonate (15 ml), 10% sodium metabisulfite (15 ml) and water (2 $\times$ 15 ml). The ether portion was dried with sodium sulfate and evaporated

under vacuum to provide crude **10** as a light yellow syrup (354 mg, 61%). The product was passed through a column (2.5 × 30 cm) packed with silica gel slurry (70 ml) in petroleum ether. Elution of the column with benzene-petroleum ether (1:1, v/v) provided pure **10** (320 mg, 55%) as an oil; nmr (carbon tetrachloride): δ 6.9-7.9 (m, 4, phenyl), 4.0-4.36 (q, 4, CH₂ of COOC₂H₅ and CH₂ of COOC₂H₅), 2.1-2.48 (q, 2, CH₂ of C₂H₅), 1.0-1.36 (t, 6, CH₃ of COOC₂H₅ and CH₃ of COOC₂H₅), 0.7-0.96 (t, 3, CH₃ of C₂H₅); ms: m/e 390 (M⁺).

Anal. Calcd. for C₁₅H₁₉IO₄: C, 46.17; H, 4.91; I, 32.52. Found: C, 46.38; H, 5.01; I, 32.36.

5-Ethyl-5-(*m*-iodophenyl)barbituric Acid (**7**) and 2-(*m*-Iodophenyl)butyric Acid (**11**).

Sodium hydride (60% oil dispersion 50 mg, 1.25 mmoles) was dissolved in absolute ethanol (5 ml). Finely powdered urea (300 mg, 5 mmoles, dried under vacuum over phosphorus pentoxide at 100°) was added and dissolved by stirring. To the clear solution was added diethyl 2-ethyl-2-(*m*-iodophenyl)malonate (**10**) (195 mg, 0.5 mmole) and the solution was protected from moisture and heated under reflux (bath temperature 82 ± 2°) for 20 hours. The solvent was evaporated under vacuum and the residue was dissolved in water (15 ml). Aqueous sodium hydroxide (1 N, 0.5 ml) was added and the solution was extracted with ether. The ether portion containing unreacted **10** was discarded. The aqueous portion was adjusted to pH 2 by adding 1 N aqueous hydrochloric acid and then extracted with ether (2 × 25 ml). The ether portion was washed with water, dried anhydrous sodium sulfate and evaporated under vacuum to provide a residue. The residue was dissolved in chloroform (2 ml) and applied to a column (2.5 × 28 cm) packed with silica gel slurry in chloroform. The column was eluted with chloroform and fractions (20 ml each) were collected. The decarboxylation product, 2-(*m*-iodophenyl)butyric acid (**11**), was initially eluted from the column and obtained (fractions 9-11) as a syrup (46 mg, 32%); nmr (deuteriochloroform): δ 8.65 [s (br), 1, COOH], 6.9-7.8 (m, 4, phenyl), 3.4 (m, 1, CH), 1.7-2.18 (q, 2, CH₂ of ethyl), 0.9 (t, 3, CH₃ of ethyl); ms: m/e 290 (M⁺).

Anal. Calcd. for C₁₀H₁₁IO₂: C, 41.40; H, 3.82; I, 43.75. Found: C, 41.57; H, 3.93; I, 43.85.

Evaporation of the later homogeneous (tlc, 2% methanol in chloroform, v/v) fractions 14-24 provided a residue which was crystallized from ether-petroleum ether to yield 55 mg (30%) of **7**, mp 203-204° (softens at 195-196°); nmr (deuteriochloroform): δ 9.32 [s (br), 2, NH and NH], 6.9-7.82 (m, 4, phenyl), 2.2-2.67 (q, 2, CH₂ of ethyl), 0.98 (t, 3, CH₃ of ethyl); ms: m/e 358 (M⁺).

Anal. Calcd. for C₁₂H₁₁IN₂O₃: C, 40.24; H, 3.10; N, 7.82; I, 35.44. Found: C, 40.43; H, 3.26; N, 7.75; I, 35.27.

5-Ethyl-5-(E-1-[¹²⁵I]iodo-1-penten-5-yl)-2-thiobarbituric Acid ([¹²⁵I]-**4**).

The procedure [4] described for the synthesis of compound **4** was used to prepare the corresponding radioiodinated analog [¹²⁵I]-**4**. A solution of **2** (30 mg, 0.1 mmole) in tetrahydrofuran (0.5 ml) was cooled in an ice-bath and shielded from light. Sodium [¹²⁵I]iodide (21.5 mCi, 15 mg, 0.1 mmole) in water (0.5 ml) was added followed by the addition of a solution of chloramine-T (45 mg, 0.2 mmole) in 50% aqueous tetrahydrofuran (1 ml). After 0.5 hour of stirring in the dark, the solution was diluted with water (10 ml) and extracted with petroleum ether (2 × 15 ml). The petroleum ether portion was washed with aqueous sodium metabisulfite solution (5%, 20 ml) followed by water (3 × 20 ml) and dried with anhydrous sodium sulfate. The petroleum ether was evaporated with argon at 35-40° to provide [¹²⁵I]-**3** (17.4 mCi, 81%), which was homogenous by tlc (chloroform:petroleum ether; 1:1, v/v). The product co-chromatographed with an authentic cold sample of **3** and was used for further reaction. Radioiodinated compound **3** was dried under vacuum at 35° (1 hour), dissolved in absolute ethanol (0.5 ml) and added to a solution of sodium hydride (60% oil dispersion, 8 mg, 0.2 mmole) and thioruea (38 mg, 0.5 mmole) in ethanol (0.5 ml). The mixture was gently refluxed (oil-bath temperature 82-85°) with exclusion of moisture for 48 hours. The solvent was evaporated with argon at ~50°. Compound [¹²⁵I]-**4** (780 μ Ci, 5%) was isolated from the residue by extraction with ethyl acetate followed by silica gel chromatographic purification as described for the correspon-

ding unlabeled analog. The radioiodinated compound co-chromatographed with the unlabeled standard on tlc analysis (5% acetone in chloroform, v/v).

5-Ethyl-5-(*m*-[¹²⁵I]iodophenyl)barbituric Acid ([¹²⁵I]-**7**) and 2-(*m*-[¹²⁵I]iodophenyl)butyric Acid ([¹²⁵I]-**11**).

Radioiodinated compounds [¹²⁵I]-**7** and [¹²⁵I]-**11** were prepared via [¹²⁵I]-**10** as described for the corresponding non-radioactive analogs **7** and **11**. Compound **8** (200 mg, 0.75 mmole) was dissolved in TFA (1.0 ml) and shielded from light. Thallium(III)trifluoroacetate (500 mg, 0.92 mmole) was added and the mixture was stirred in the dark at 70° for 64 hours. The reaction solution was cooled to room temperature and potassium [¹²⁵I]iodide (25.7 mCi, 850 mg, 5.1 mmoles) in water (2.5 ml) was added with vigorous stirring which was continued for 1 hour. Ether (25 ml) and water (10 ml) were added, the mixture partitioned and the ether layer was separated. The ether portion was cautiously poured into a stirred saturated sodium bicarbonate solution (20 ml). The ether portion was separated, washed with 5% sodium metabisulfite solution (10 ml) followed by water and dried with anhydrous sodium sulfate. Evaporation of ether provided 1.4 mCi (5.4%) of crude [¹²⁵I]-**10** which was purified by silica gel column chromatography as described for nonradioactive compound **10**. Recovery of anhydrous [¹²⁵I]-**10** after column chromatography was 72% (1.0 mCi). The activity, [¹²⁵I]-**10** was dissolved in absolute ethanol (2 ml) and added to a solution of urea (300 mg, 5 mmoles) and sodium hydride (60% dispersion, 40 mg, 1 mmole) absolute ethanol (0.5 ml). The mixture was refluxed (oil-bath temperature 82-85°) with exclusion of moisture for 16 hours. The solvent was evaporated under argon at ~50°. The radioiodinated compounds [¹²⁵I]-**7** (298 μ Ci, 30%) and [¹²⁵I]-**11** (317 μ Ci, 32%) were isolated from the residue by ether extraction followed by chromatographic purification as described for the corresponding unlabeled analogs. The radioiodinated compounds were homogenous when co-chromatographed with the respective standards upon tlc analysis.

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