cation was achieved on an ion-exchange column eluted with 200 mL each of 1.5, 2, and 2.5 N HCl prior to removal of the product with 250 mL of 3 N HCl. Solvent evaporation, followed by recrystallization as described for **3**, produced pale yellow needles of **4** in 40–50% yield: UV λ_{max} (0.1 N $HClO_4$) 268 nm (ϵ 5.44), 260 (6.35), 254 (7.02); IR (KBr) 1760, 1180 cm^{-1}. Anal. ($C_{10}H_{30}N_7Cl_4O_2SRu \cdot H_2O$) C, H, N, S.

Ruthenium-103 Complexes. Radiolabeled [^{103}Ru]chloropentaammineruthenium dichloride was synthesized according to a literature procedure[29] from 400 mg of $RuCl_3 \cdot H_2O$ containing 1.5 mCi ($^{103}RuCl_3$). After two recrystallizations from boiling 0.1 N HCl, 80–100 mg of product was obtained as bright orange crystals with a calculated specific activity of 3.0 μCi/mg of complex. Complexes 1–4 were then prepared according to the above procedures from equal amounts of radioactive and cold pentaammine complex. The identity of each crystalline complex obtained was confirmed by comparison of IR and electronic spectra with those of previously prepared unlabeled samples having satisfactory elemental analyses. Final specific activities of the ^{103}Ru-labeled complexes were approximately 1.0 μCi/mg of complex.

Tissue Distribution Studies. The ^{103}Ru-labeled complexes (10 μCi) were dissolved in 1 mL of saline solution just prior to use and injected (0.05–0.1 mL) into the tail vein of normal mice. After the desired time interval, the animals were sacrificed by ether asphyxiation, and the organs of interest were removed, weighed, and counted in a NaI(Tl) scintillation spectrometer. The activity observed in each organ was converted to percent injected dose per organ (% ID/organ) and/or per gram of organ (% ID/g). Data from the injection of different preparations of ^{103}Ru-labeled complexes were analyzed separately and were found to agree within experimental error.

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Registry No. **1**, 84800-85-1; **1**-^{103}*Ru*, 84800-88-4; **2**, 84823-40-5; **2**-^{103}*Ru*, 84809-56-3; **3**, 84800-86-2; **3**-^{103}*Ru*, 84800-89-5; **4**, 84800-87-3; **4**-^{103}*Ru*, 84800-90-8; **6**, 18532-87-1; **7**, 66402-61-7; [^{103}Ru]-chloropentaammineruthenium dichloride, 78713-16-3.

Potential Cerebral Perfusion Agents: Synthesis and Evaluation of a Radioiodinated Vinylalkylbarbituric Acid Analogue

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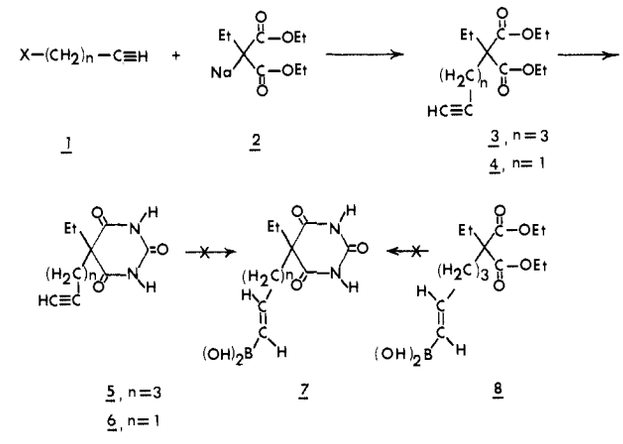
A new iodinated barbiturate has been prepared. Treatment of 5-chloropentyne and propargyl bromide with diethyl 2-ethyl-2-sodiomalonate (DESM) provided diethyl 2-ethyl-2-(1-pentyn-5-yl)malonate (**3**) and diethyl 2-ethyl-2-propargylmalonate (**4**), respectively. Similar condensation of DESM with (*E*)-(5-iodo-1-penten-1-yl)boronic acid (**9**) or the reaction of catecholborane with **3** provided diethyl (*E*)-2-ethyl-2-(1-borono-1-penten-5-yl)malonate (**8**). The direct sodium iodide–chloramine-T iodination of **8** or the treatment of (*E*)-1,5-diiodo-1-pentene (**10**) with DESM provided diethyl (*E*)-2-ethyl-2-(1-iodo-1-penten-5-yl)malonate (**11**). The condensation of functionalized malonates **3**, **4**, and **11** with urea in the presence of a base provided the corresponding barbiturates, 5-ethyl-5-(1-pentyn-5-yl)- (**5**), 5-ethyl-5-propargyl- (**6**), and (*E*)-5-ethyl-5-(1-iodo-1-penten-5-yl)barbituric acid (**12**), respectively. (*E*)-6-(Ethoxycarbonyl)-1-iodo-1-octene-6-carboxylic acid (**13**) was isolated as the hydrolytic byproduct of **11**. Compound **13** decarboxylated under vacuum to provide ethyl (*E*)-1-iodo-1-octene-6-carboxylate (**14**). The ^{125}I-labeled congeners of **12** and **13** were synthesized in the same manner and evaluated in rats. The barbiturate **12** exhibited significant brain uptake (~1% dose after 5 min), demonstrating that iodinated barbiturates freely cross the intact blood–brain barrier.

Radiolabeled agents that penetrate the blood–brain barrier[1] can potentially be used to monitor regional cerebral blood perfusion. Certain lipid-soluble[2] and pH shift agents[3-5] freely cross the intact blood–brain barrier and have been evaluated as cerebral perfusion agents. Recently, the synthesis and preliminary animal testing of *N*-isopropyl-*p*-[^{123}I]iodoamphetamine has been reported,[6,7] and this agent has been used to measure cerebral perfusion in patients with single-photon emission computed tomography.[8,9] Barbiturates are another group of lipophilic agents that freely cross the blood–brain barrier, as indicated by studying ^{11}C-labeled[10] and 5-substituted[11] ^{75}Se-

Scheme I



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and ^{123m}Te-labeled barbituric acid analogues.

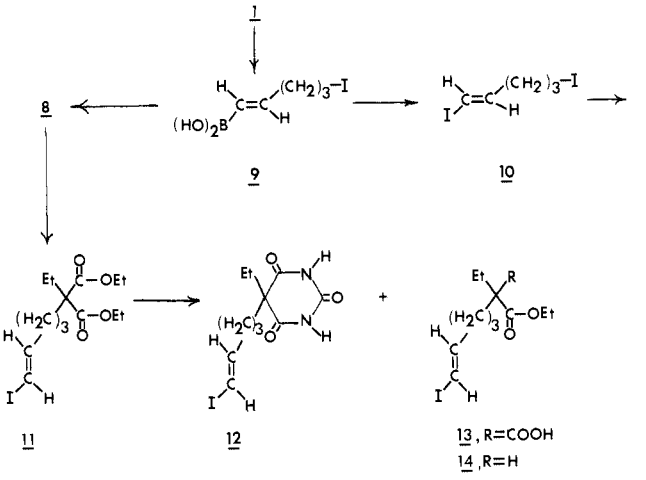
We have now synthesized a model iodovinylbarbituric acid analogue for tissue distribution studies to assess the potential utility of such compounds as cerebral perfusion agents. The vinyl iodides are also chemically stable and would be expected to have advantage over similar alkyl iodides, which are prone to facile in vivo deiodination.[12]

Chemistry. The classical route for the synthesis of barbiturates involves condensation of a substituted malonic acid ester with urea in the presence of sodium ethoxide (NaOEt). A wide variety of barbituric acid analogues can be prepared by using suitably functionalized malonic acid ester substrates.[13,14] Condensation with a stronger base, such as potassium *tert*-butoxide (*t*-BuOK) in dimethyl sulfoxide has also been reported.[15] With this latter method, yields of the barbiturates can often be improved and the formation of certain side products can be avoided.

Various approaches for the introduction of a terminal alkynyl chain at position 5 of the barbiturate moiety and the synthesis of a model iodovinyl-substituted barbiturate, (*E*)-5-ethyl-5-(1-iodo-1-penten-5-yl)barbituric acid (**12**), are described in this paper. Our initial approach (Scheme I) consisted of the reaction of a haloalkyne with diethyl 2-ethyl-2-sodiomalonate (DESM, **2**) generated in situ via the treatment of diethyl ethylmalonate with sodium hydride in dimethylformamide (DMF). Thus, diethyl 2-ethyl-2-(1-pentyn-5-yl)malonate (**3**, n = 3) and diethyl 2-ethyl-2-propargylmalonate (**4**, n = 1) were prepared with 5-chloropentyne[16] (1, X = Cl; n = 3) and propargyl bromide (1, X = Br; n = 1), respectively. Following purification by vacuum distillation, ring annulation of these diethyl ethylalkynylmalonates with urea in the presence of potassium *tert*-butoxide in Me_2SO provided the desired 5-ethyl-5-(1-pentyn-5-yl)barbituric acid (**5**, n = 3) and 5-ethyl-5-propargylbarbituric acid (**6**, n = 1), respectively. The compounds were characterized by proton nuclear magnetic resonance (^{1}H NMR) and elemental analyses.

Alkynes react with catecholborane to give vinylboronic acids, which can then be iodinated with iodine chloride[16-18] or sodium iodide and chloramine-T[19,20] to provide the corresponding vinyl iodides. Following similar procedures, our attempts for the addition of catecholborane on **5** and **6** to provide the corresponding barbiturate vinylboronic acids **7** (n = 1 or 3) were unsuccessful. This was probably due to the reactivity of catecholborane with the NH or OH groups of the ring system. Using a different route (Scheme I), we pursued reaction of catecholborane with a terminal alkyne substituted diethylmalonate intermediate. Treatment of the pentynylmalonate **3** with catecholborane under nitrogen atmosphere gave diethyl (*E*)-2-ethyl-2-(1-borono-1-penten-5-yl)malonate (**8**) in 40% yield. However, compound **8** failed to provide the desired ring annulation product **7** when treated with urea in the presence of a base (NaOEt or *t*-BuOK) and resulted in the formation of unidentified hydrolytic products.

Scheme II



Alternatively, a second approach for the synthesis of **12** via diethyl (*E*)-2-ethyl-2-(1-borono-1-penten-5-yl)malonate (**8**) and diethyl (*E*)-2-ethyl-2-(1-iodo-1-penten-5-yl)-malonate (**11**) was followed (Scheme II). Treatment of 5-iodopentyne[21] with catecholborane under nitrogen atmosphere provided crystalline (*E*)-(5-iodo-1-penten-1-yl)boronic acid[21] (**9**). This acid was condensed with DESM in DMF to provide intermediate **8** (67%) after chromatographic purification. The condensation of the iodo derivative **9** with DESM proceeded very smoothly at room temperature because of the greater susceptibility of the iodo compound to nucleophilic attack by the anion of **2**. This method provided a better yield of **8** than that obtained from **3**. The samples of **8** obtained from **3** or **9** were identical by TLC and NMR analyses.

Following a different route, we first iodinated compound **9** using iodine chloride to provide (*E*)-1,5-diiodo-1-pentene[21] (**10**), which was then treated with DESM to yield **11** as an oil. Alternatively, compound **11** was obtained via direct iodination of boronic acid **8** with sodium iodide and chloramine-T in aqueous THF. The samples of **11** obtained from both procedures were identical by TLC and NMR analyses. The treatment of iodo compound **11** with urea in the presence of *t*-BuOK in Me_2SO did not provide the expected iodovinylbarbiturate **12**. Instead, simultaneous dehydroiodination occurred with ring annulation to provide the alkynyl barbiturate **5**, which was identified by comparison with an authentic sample of **5** obtained from **3**. Using a relatively mild base (NaOEt), we accomplished successful ring annulation of **11** with urea in boiling ethanol to provide the desired (*E*)-5-ethyl-5-(1-iodo-1-penten-5-yl)barbituric acid (**12**), which was separated from a second product by silica gel column chromatography. The second product was also isolated and identified as (*E*)-6-(ethoxycarbonyl)-1-iodo-1-octene-6-carboxylic acid (**13**), which probably resulted from the partial hydrolysis of the iodovinyl ester **11**. The NMR spectrum of **13** was consistent with this structure. The facile decarboxylation[15] of this compound occurred during drying under vacuum prior to

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Table I. Distribution of Radioactivity in Tissues of Fischer 344 Female Rats following Intravenous Administration of (*E*)-5-Ethyl-5-(1-[^{125}I]iodo-1-penten-5-yl)barbituric Acid[a]

time after injection	mean % injected dose/g (range)						brain/blood (mean)
	brain	blood	thyroid	liver	heart	lung	
2 min	0.83 (0.77-0.97)	1.00 (0.88-1.15)	7.64 (6.65-8.08)	3.19 (2.91-3.53)	1.49 (1.35-1.55)	1.31 (1.17-1.42)	0.83
5 min	0.82 (0.74-0.94)	0.90 (0.81-1.00)	6.84 (6.19-7.22)	2.69 (2.49-2.82)	1.23 (1.13-1.29)	1.08 (0.98-1.22)	0.91
30 min	0.33 (0.25-0.37)	0.92 (0.68-1.03)	26.16 (18.74-30.84)	1.21 (0.97-1.41)	0.71 (0.55-0.82)	0.79 (0.65-0.87)	0.36
1 h	0.19 (0.18-0.22)	0.97 (0.90-1.03)	73.0 (53.0-96.0)	0.82 (0.71-0.93)	0.56 (0.50-0.63)	0.72 (0.66-0.77)	0.20
2 h	0.10 (0.08-0.13)	0.76 (0.71-0.87)	130.0 (92.0-159.0)	0.50 (0.42-0.62)	0.33 (0.24-0.38)	0.52 (0.47-0.58)	0.14
4 h	0.03 (0.03-0.04)	0.46 (0.45-0.48)	178.0 (156.0-207.0)	0.21 (0.19-0.23)	0.18 (0.16-0.20)	0.29 (0.28-0.31)	0.07
1 day	0.007 (0.007-0.008)	0.03 (0.03-0.03)	434.0 (406.0-499.0)	0.02 (0.02-0.02)	0.02 (0.02-0.02)	0.02 (0.02-0.03)	0.26

[a] Four rats were used each time period. Other tissues analyzed were spleen, kidney, fat, and muscle. Each rat received 7.95 μCi of the ^{125}I-labeled barbiturate (sp act. ~155 mCi/mmol) in phosphate buffer (pH 7.4), administered by injection in a lateral tail vein.

elemental analyses. The carbon, hydrogen, iodine, and oxygen analyses were consistent with the structure of the decarboxylated product, ethyl (*E*)-1-iodo-1-octene-6-carboxylate (**14**). Compounds **1-13** were synthesized in pure form and characterized by TLC, NMR, MS, and elemental analyses. The ^{125}I-labeled analogues of **11–13** were prepared by the same methods and purified by silica gel column chromatography.

Biological Evaluation. The tissue distribution and brain uptake of the radioiodinated compounds, (*E*)-5-ethyl-5-(1-[^{125}I]iodo-1-penten-5-yl)barbituric acid (**12**) and (*E*)-6-(ethoxycarbonyl)-1-[^{125}I]iodo-1-octene-6-carboxylic acid (**13**), were evaluated in female Fischer 344 rats. Four animals were used for each time period, ranging from 2 min to 1 day, and the values for brain, blood, thyroid, liver, heart, and lung were determined. The data for compound **12** (Table I) indicate rapid and significant brain uptake of radioactivity within 2 to 5 min, providing a brain blood ratio of ~1. A gradual washout then began, and radioactivity was nearly absent at the end of day 1 from all the organs tested, except from the thyroid where a drastic increase in the radioactivity was observed. Also excised were spleen, kidney, fat, and muscle, which accumulated a maximum percent injected dose per gram of g tissue value of 0.79 (5 min), 1.60 (2 min), 1.01 (30 min), and 0.50 (5 min), respectively. Most of the activity (~70%) was secreted via urine and feces at the end of day 3. The accumulation of radioactivity in the thyroid results from in vivo deiodination of barbiturate **12**.

In contrast to the iodovinylbarbiturate **12**, the iodovinyl carboxylic acid **13** showed no significant uptake in the thyroid or any of the other tissues examined and, thus, appears to be resistant toward in vivo deiodination. Recent studies in this laboratory have demonstrated the low in vivo deiodination of 18-[^{125}I]iodo-13-tellura-17-octadecenoic acid.[21] Other studies have reported that (*E*)-17α-[^{125}I]-iodovinylestradiol is stable to deiodination.[22] Our studies indicate that the iodovinylalkylbarbiturate does cross the blood–brain barrier, and similar compounds may prove good candidates for evaluation as potential cerebral perfusion agents. The unexpected in vivo deiodination of **12** could be overcome by attachment of iodine to a stable system, such as a phenyl ring, on a barbituric acid. The synthesis of such a model compound, 5-ethyl-5-(3-iodo-4-hydroxyphenyl)barbituric acid, has already been reported.[23]

Experimental Section

The melting points (mp) were determined in capillary tubes with a Buchi SP apparatus and are uncorrected. Thin-layer chromatographic analyses (TLC) were performed with 250-μm 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. The low-resolution mass spectra (MS) were recorded at 70 eV with a Kratos MS 25 instrument. The proton nuclear magnetic resonance spectra (^{1}H 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 D_2O followed by reintegration of the NMR spectrum. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Where analyses are indicated by only the symbol of the elements, the analytical results for those elements were within ±0.4% of the theoretical value.

Materials. Dimethylformamide (DMF) was analytical grade and was stored over 4A molecular sieves 24 h prior to use. All other chemicals and solvents were analytical grade and were used without further purification. The sodium [^{125}I]iodide was purchased from New England Nuclear, Inc. (North Billierica, MA). The specific activity of the no-carrier-added radioiodide was adjusted to 48.7 mCi/mmol prior to use. The 1-chloro-4-pentyne was purchased from K&K Laboratories, Inc. (Plainview, NY).

Animal Tissue Distribution Experiments. The distribution of radioactivity was determined in tissues of 10–12 week old female Fischer 344 rats (170–200 g) after intravenous administration of ^{125}I-labeled compounds **12** and **13**. 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 22-μm Millipore filter and injected via a lateral tail vein into the ether-anesthetized animals. The animals were anesthetized with ether and killed by cervical fracture. The organs were excised, rinsed with saline solution, blotted dry, placed in tared vials, and weighed. The radioactive contents were determined in a Packard autogamma counter, and the percent injected dose per gram of tissue values were then calculated.

Diethyl 2-Ethyl-2-(1-pentyn-5-yl)malonate (3). Diethyl 2-ethyl-2-sodiomalonate (DESM) was freshly generated by dropwise (0.5 h) addition of diethyl ethylmalonate (9.41 g, 50

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mmol) to a suspension of NaH (60% oil dispersion, 20 g, 50 mmol) in anhydrous DMF (20 mL). A clear, oily solution of DESM was obtained after the evolution of hydrogen had ceased (~1 h). 5-Chloro-1-pentyne (5.17 g, 50 mmol) was added, and the mixture stirred at 60–65 °C (bath temperature) for 20 h with exclusion of moisture. The reaction mixture was diluted with H_2O (100 mL) and extracted with ethyl ether (2 × 100 mL). The combined ether portion was washed with H_2O and dried over anhydrous $NaSO_4$, and the solvent was evaporated in vacuo to provide **3** as an oil. Distillation under vacuum gave 9.0 g (79%) of **3**: bp 74–76 °C (1.5 mm); ^1H NMR ($CDCl_3$) δ 4.2 (q, J = 7 Hz, 4, 2 CH_2 of 2 $COOC_2H_5$), 2.4–1.73 [m, 7, $HC{\equiv}C(CH_2)_3$], 1.7–1.47 (m, 2, CH_2 of C_2H_5), 1.27 (t, J = 7 Hz, 6, 2 CH_3 of 2 $COOC_2H_5$), 0.83 (t, 3, CH_3 of C_2H_5); MS, m/e 255 (M^+). Anal. ($C_{14}H_{22}O_4$) C, H.

Diethyl 2-Ethyl-2-(1-propyn-3-yl)malonate (4). Diethyl ethylmalonate (18.8 g, 100 mmol) was added dropwise (0.5 h) to a stirred suspension of NaH (60% oil dispersion, 4.0 g, 100 mmol) in anhydrous DMF (25 mL). After about 1 h, the evolution of hydrogen had ceased, and a solution (80%) of propargyl bromide in toluene (10.0 mL, ~100 mmol) was added dropwise (15 min). The reaction mixture was allowed to stir overnight at room temperature, diluted with H_2O (125 mL), and extracted with ethyl ether (100 mL × 2). The combined ether portion was washed with H_2O (100 mL), dried (Na_2SO_4), and evaporated in vacuo to provide crude **4** as an oil. Distillation of the product under vacuum provided 18 g (80%) of pure **4**: bp 72.5–74.5 °C (1.5 mm); ^1H NMR (CCl_4) δ 4.0–4.4 (q, J = 7 Hz, 4, 2 CH_2 of 2 $COOC_2H_5$), 2.73 (d, J = 2.5 Hz, 2, CH_2 of propynyl), 1.8–2.26 (m, 3, CH_2 of ethyl and CH of propynyl), 1.25 (t, J = 7 Hz, 6, 2 CH_3 of 2 $COOC_2H_5$), 0.85 (t, J = 7.5 Hz, 3, CH_3 of ethyl). Anal. ($C_{12}H_{18}O_4$) C, H.

2-Ethyl-2-(1-pentyn-5-yl)barbituric Acid (5). Method A. A solution of diethyl 2-ethyl-2-(1-pentyn-5-yl)malonate (**3**; 550 mg, 2.17 mmol) in Me_2SO (2 mL) was added to a solution of urea (5 g, 83.3 mmol) and t-BuOK (500 mg, 4.46 mmol) in Me_2SO (23 mL). The solution was stirred at room temperature under anhydrous conditions for 24 h, diluted with H_2O (100 mL), and adjusted to pH 10 by addition of 1 N NaOH. The solution was extracted with ethyl ether (2 × 50 mL), which was discarded. The aqueous portion was adjusted to pH 2 by addition of 1 N HCl, and extracted with ethyl ether (2 × 50 mL). The combined ether portion was washed with H_2O (50 mL) and dried (Na_2SO_4). Crystallization from C_6H_6 gave 200 mg (42%) of pure **5**: mp 101 °C; ^1H NMR ($CDCl_3$ + CD_3OD) δ 9.2 (br s, 2, NH and NH), 1.9–2.3 [m, 6, $(CH_2)_3$], 1.25–1.75 (m, 3, HC≡C of propynyl and CH_2 of ethyl), 0.9 (t, J = 5 Hz, 3, CH_3 of ethyl). Anal. ($C_{11}H_{14}N_2O_3$) C, H, N.

Method B. In an attempt to synthesize **12**, compound **11** (382 mg, 1 mmol) was stirred in a solution of urea (300 mg, 5 mmol) and t-BuOK (226 mg, 2.1 mmol) in Me_2SO (10 mL) at room temperature for 24 h. The solution was diluted with H_2O, adjusted to pH 2 with dilute HCl, and extracted with ethyl ether. The ether layer was washed with H_2O, and dried over anhydrous Na_2SO_4. Evaporation of the ether provided a product that was identical with **5** (TLC and ^1H NMR) obtained by method A: yield 70 mg (~32%).

2-Ethyl-2-(1-propyn-3-yl)barbituric Acid (6). The intermediate **4** (3.0 g, 13.3 mmol) was added to a stirred solution of t-BuOK (3.0 g, 26.8 mmol) and urea (20.0 g, 333.3 mmol) in Me_2SO (100 mL). The solution was stirred at room temperature under anhydrous conditions for 24 h, and the product **6** was isolated as described for the corresponding pentynyl derivative **5**: yield 600 mg (24%); mp 203 °C; ^1H NMR (Me_2CO-d_6) δ 10.42 (br s, 2, NH and NH), 2.76 (d, J = 2.5 Hz, 2, CH_2 of propynyl), 2.53 (t, J = 2.5 Hz, 1, HC≡C of propynyl), 1.9 (q, J = 7.5 Hz, 2, CH_2 of ethyl), 0.82 (t, J = 7.5 Hz, 3, CH_3 of ethyl). Anal. ($C_9H_{10}N_2O_3$) C, H, N.

Diethyl (*E*)-2-Ethyl-2-(1-borono-1-penten-5-yl)malonate (8). Method A. Diethyl 2-ethylmalonate (15.4 g, 30 mmol) was added cautiously to a stirred suspension of NaH (60% oil dispersion, 1.2 g, 30 mmol) in anhdrous DMF (10.0 mL). (*E*)-(5-iodo-1-penten-1-yl)boronic acid (**9**; 3.6 g, 15 mmol) was added to the clear oily solution after the evolution of hydrogen had ceased. Almost immediate precipitation occurred. The mixture was stirred at room temperature for 20 h and poured into a mixture of ethyl ether (50 mL) and H_2O (50 mL). The aqueous portion was adjusted to pH 5 by the addition of dilute H_2SO_4, and the mixture was extracted with ether (2 × 50 mL). The combined ether portion was washed with H_2O, dried (Na_2SO_4), and evaporated under vacuum (temperature <30 °C). The crude product (syrup) was passed through a column (40 × 3 cm) packed with a silica gel slurry in $CHCl_3$. The column was eluted with $CHCl_3$ to provide pure **8** as a colorless oil: yield 3.0 g (67%); ^1H NMR ($CDCl_3$) δ 6.5 (doublet of triplets, J = 6 and 18 Hz, 1, pentenyl C_2 H), 5.5 (d, J = 18 Hz, 1, pentenyl C_1 H), and other protons; MS, m/e 300 (M^+).

Method B. Catecholborane (0.13 mL, ~1.4 mmol) was added with stirring to an argon-flushed flask containing diethyl 2-ethyl-2-(1-pentyn-5-yl)malonate (**3**; 313 mg, 1.25 mmol). The solution turned pale yellow and was allowed to stir for 16 h at room temperature with exclusion of moisture. Water (2 mL) was added, and the mixture was stirred for an additional 6 h at room temperature. The mixture was diluted with H_2O and extracted with ethyl ether (2 × 25 mL). The combined ether portion was washed with H_2O, dried (Na_2SO_4), and evaporated in vacuo. The residue (syrup) was passed through a column (2.5 × 30 cm) packed with a silica gel slurry in $CHCl_3$. The column was eluted with $CHCl_3$ to provide 150 mg (40%) of **8**, which was identical (TLC and ^1H NMR) with **8** obtained by method A.

Diethyl (*E*)-2-Ethyl-2-(1-iodo-1-penten-5-yl)malonate (11). Method A. A solution of **8** (600 mg, 2 mmol) in THF (4 mL) was cooled (0 °C) with stirring and shielded from light. Sodium iodide (300 mg, 2 mmol) was dissolved in H_2O (4 mL) and added followed by the addition of a solution of chloramine-T (900 mg, 4 mmol) in 50% aqueous THF (8 mL). The reaction mixture immediately turned orange and was stirred in an ice bath (~5 °C) for 0.5 h. The colorless solution was diluted with H_2O (50 mL) and extracted with petroleum ether (2 × 50 mL). The combined petroleum ether portion was washed with a 5% aqueous solution (50 mL) of sodium metabisulfite followed by H_2O (2 × 50 mL), and dried (Na_2SO_4). Evaporation of the petroleum ether in vacuo provided **11** (530 mg, 69%) as an oil. This material was of sufficient purity for further reaction. The analytical sample was obtained by following two different procedures: A, vacuum distillation, bp 140–142 °C (1.5 mm); B, chromatographic purification with a silica gel column and 25% $CHCl_3$ in petroleum ether as the eluting solvent. NMR (CCl_4) δ 5.8–6.7 (m, 2, CH=CHI) and other protons; MS, m/e 382 (M^+). Anal. ($C_{14}H_{23}O_4I$) C, H, I.

Method B. The (*E*)-1,5-diiodo-1-pentene (**10**; 966 mg, 25 mmol) was added to a solution of DESM, which was generated (see the Experimental Section for **3**) by the addition of diethyl 2-ethylmalonate (565 mg, 3 mmol) and NaH (60% oil dispersion, 120 mg, 3 mmol) in DMF (1.2 mL). The reaction mixture was stirred at ambient temperature for 15 h in the dark and then diluted with H_2O (50 mL). The solution was adjusted to pH 5 by adding dilute HCl and extracted with petroleum ether. Product **11**, isolated as described in method A, was identical (TLC and ^1H NMR) with an authentic sample of **11** obtained by method A.

(*E*)-5-Ethyl-5-(1-iodo-1-penten-5-yl)barbituric Acid (12) and (*E*)-6-(Ethoxycarbonyl)-1-iodo-1-octene-6-carboxylic Acid (13). Finely powdered urea (300 mg, 5 mmol, dried under vacuum over P_2O_5 at 100 °C) was added to a solution of NaH (60% oil dispersion, 120 mg, 3 mmol) in absolute ethanol (10 mL). To the clear solution was added **11** (382 mg, 1 mmol), and the solution was refluxed (bath temperature 85–90 °C) for 24 h with exclusion of moisture. The solvent was evaporated under vacuum, and the residue was dissolved in H_2O (20 mL) and 1 N NaOH (0.5 mL). The solution was extracted with ethyl ether (~50 mL). The ether portion was discarded. The aqueous portion was adjusted to pH 2 with 1 N HCl and extracted with ethyl ether (2 × 25 mL). The combined ether portion was washed with H_2O and dried (Na_2SO_4). Evaporation of the ether under vacuum provided a residue, which was passed through a column (2.5 × 30 cm) packed with a silica gel slurry (~75 mL) in $CHCl_3$. The column was eluted with $CHCl_3$, and 40 fractions (20 mL each) were collected. The hydrolyzed product **13** was eluted first from the column and was obtained as a syrup by evaporating fractions 18–22, which moved as a streak on TLC (solvent 5% acetone in $CHCl_3$, v/v): yield 168 mg (47%); ^1H NMR ($CDCl_3$) δ 11.7 (s, 1, COOH), 5.85–6.7 (m, 2, ICH=CH), 4.2 (q, J = 7 Hz, 2, CH_2 of $COOC_2H_5$), 1.1–2.3 (m and t, 8 and 3, pentenyl methylenes, CH_2 of ethyl, and CH_3 of $COOC_2H_5$), 0.82 (t, J = 7 Hz, 3, CH_3 of ethyl). The compound decarboxylated upon drying under vacuum prior to elemental

analysis to give ethyl (*E*)-1-iodo-1-octene-6-carboxylate (**14**). Anal. $C_{11}H_{19}O_2I$) C, H, I, O.

Evaporation of fractions 25–35 (single compact spot on TLC, solvent 5% acetone in $CHCl_3$, v/v) under vacuum provided a residue, which was crystallized from a solution of 5% $CHCl_3$ in CCl_4 to yield 110 mg (31%) of **12** as a white crystalline product: mp 158–159 °C; ^1H NMR ($CDCl_3$) δ 9.1 (br s, 2, NH and NH), 5.9–6.7 (m, 2, I CH=), 1.1–2.3 (m and m, 6 and 2, pentenyl methylenes and CH_2 of ethyl), 0.9 (t, 3, CH_3 of ethyl). Anal. ($C_{11}H_{15}N_2O_3I$) C, H, N, I.

(*E*)-5-Ethyl-5-(1-[^{125}I]iodo-1-penten-5-yl)barbituric Acid ([^{125}I]12) and (*E*)-6-(Ethoxycarbonyl)-1-[^{125}I]iodo-1-octene-6-carboxylic Acid ([^{125}I]13). Radioiodinated compounds [^{125}I]**12** and [^{125}I]**13** were prepared via **11** (method A) as described for the corresponding nonradioactive analogues **12** and **13**. A solution of **8** (30 mg, 0.1 mmol) in THF (0.5 mL) was cooled in an ice bath and shielded from light. Sodium [^{125}I]iodide (15.5 mCi, 15 mg, 0.1 mmol) in H_2O (0.5 mL) was added, followed by the addition of a solution of chloramine-T (45 mg, 0.2 mmol) in 50% aqueous THF (1 mL). After 0.5 h of stirring in the dark, the solution was diluted with H_2O (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 H_2O (2 × 20 mL), and dried (Na_2SO_4). The petroleum ether was coevaporated with argon at 35–40 °C. The residue was passed through a column (1.2 × 30 cm) packed with a silica gel slurry (75 mL) in petroleum ether. The column was eluted with a 50% (v/v) solution of petroleum ether in $CHCl_3$ to provide [^{125}I]**11** (9.28 mCi, 61.4%), which was identical on silica gel TLC ($CHCl_3$; petroleum ether; 1:1, v/v) with an authentic cold sample of **11**. [^{125}I]**11** was dried under vacuum at 35 °C (1 h), dissolved in absolute ethanol (0.5 mL), and added to a solution of NaH (60% oil dispersion, 8 mg, 0.2 mmol) and urea (30 mg, 0.5 mmol) in ethanol (0.5 mL). The mixture was gently refluxed (oil-bath temperature 82–85 °C) with exclusion of moisture for 36 h. The solvent was coevaporated with argon at ~50 °C. Compounds [^{125}I]**12** (1.39 mC, 15%) and [^{125}I]**13** (3.7 mCi, 40%) were isolated from the residue by ethyl ether extraction, followed by chromatographic purification as described for the corresponding unlabeled analogues. The radioiodinated compounds cochromatographed with the unlabeled standard upon TLC analysis.

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Sulfur Analogues of Psychotomimetic Agents. 2. Analogues of (2,5-Dimethoxy-4-methylphenyl)- and (2,5-Dimethoxy-4-ethylphenyl)isopropylamine

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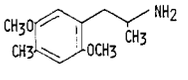
The two thio analogues of each of the well-known psychotomimetic drugs DOM [(2,5-dimethoxy-4-methylphenyl)isopropylamine] and DOET [(2,5-dimethoxy-4-ethylphenyl)isopropylamine] have been synthesized and pharmacologically evaluated in man. The 5-thio isomers are more potent as psychotomimetic agents than the 2-thio isomers but still represent a drop of an order of magnitude in potency from the sulfur-free counterparts. The dithio analogue of DOM was synthesized and found to be without central activity at a dosage of ~50 times the mean effective dose of DOM.

Of the large number of alkoxy-substituted phenethylamines that are known to be psychotomimetic in man,[1] only a few analogues with a sulfur atom replacing an oxygen atom have been prepared and evaluated pharmacologically.

Mescaline, the principal centrally active component from the cactus *Anhalonium lewinii*, contains three oxygen atoms, and the two possible thio analogues of it [3-(methylthio)-4,5-dimethoxyphenethylamine and 4-(methylthio)-3,5-dimethoxyphenethylamine] have been shown to be more potent as psychotomimetic agents.[2] The potent psychotomimetic agent (2,4,5-trimethoxyphenyl)isopropylamine (TMA-2) also contains three oxygen atoms. All three possible thio analogues of it have also been prepared,[3,4] but it is only the 4-thio analogue that exceeds the parent drug in central activity.[5] The centrally inactive positional isomer of mescaline, 2,3,4-trimethoxyphenethylamine (isomescaline) has three possible sulfur analogues, not one of which is active.[2] From these limited data, no generalities can be made concerning the pharmacological consequences of sulfur for oxygen substitution.

(2,5-Dimethoxy-4-methylphenyl)isopropylamine (DOM, **1**) and its 4-ethyl homologue (DOET, **2**) are among the



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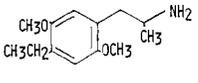

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more potent phenethylamine psychotomimetics known.[6] Each can give rise to two possible thio analogues, with 2- or 5-sulfur substitution. It was felt that their preparation

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