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Synthesis and Antihypertensive Activity of Some Ester Progenitors of Methyldopa

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A variety of esters of methyldopa was synthesized with the objective of obtaining derivatives that would be more efficiently absorbed from the gastrointestinal tract than the free amino acid and would undergo conversion to methyldopa readily in the blood or target tissues. Two of the esters, α-pivaloyloxyethyl (**4u**) and α-succinimidoethyl (**4w**), were found to be more potent antihypertensive agents than methyldopa in animal models and were selected for further study in man. The amino esters were prepared by three different methods, including direct esterification of methyldopa without the use of N- or O-protecting groups.

Methyldopa (1) is an effective, orally active antihypertensive agent which has found wide use for the reduction of blood pressure in hypertensive subjects. In an attempt to enhance oral absorption and thereby improve antihypertensive potency, a variety of methyldopa derivatives was synthesized with the objective of obtaining compounds that would be more efficiently absorbed from the gastrointestinal tract than the free amino acid and would undergo conversion to methyldopa readily in the blood or target tissues. Of these derivatives, several novel esters of methyldopa were found to have antihypertensive activity in the spontaneously hypertensive (SH) rat. Two esters, **4u** and **4w**, which exhibited good oral absorption and were particularly potent in hypertensive animal models, were selected for further study in man. This report describes the synthesis of some methyldopa esters and their evaluation as antihypertensive agents in the SH rat.

Chemistry. The acid **2b**, in which the catechol and amino functions of methyldopa are protected as the diphenyl ketal[1] and the benzylcarbamate, respectively, could be prepared easily from **1** in 52% overall yield. Initial attempts to esterify **2b** through carboxyl activation, e.g., with dicyclohexylcarbodiimide, and subsequent reaction with alcohols were generally unsuccessful. This is probably

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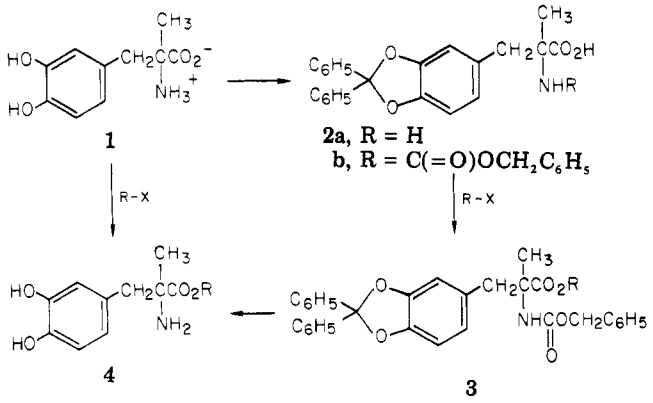


due to the α-methyl and *N*-Cbz groups which provide sufficient steric hindrance to discourage reaction at the carboxyl carbonyl.

However, **2b** could be esterified to **3** by alkylation of its triethylamine salt in DMF with suitable halides. In this method, reaction occurs at a position one atom removed from the carboxyl carbon and therefore is less subject to steric hindrance. This esterification procedure, developed originally by Schwyzer,[2] has been applied recently to the synthesis of esters of hindered carboxylic acids.[3] Removal of the amino and catechol blocking groups of **3** under catalytic hydrogenation conditions led to the esters **4** in satisfactory overall yields (Tables I and II).

Alternatively, direct alkylation of the unprotected amino acid, presumably as the dipolar ion **1**, in a polar, aprotic solvent such as DMF, Me_2SO, or HMPA proved to be a more convenient route to the α-methylamino esters.[4] Esters **4a,p,s,v** were prepared by this one-step procedure in 37–61% yields. That only modest yields were obtained in this reaction is probably a consequence of the fact that in these solvents the starting acid anion, **1**, is generally a stronger base than the resulting amino ester. As a result, the esterification reaction does not proceed to completion because the remaining amino acid anion becomes protonated as the reaction proceeds.

Two esters, the 2-acetamidoethyl (**4f**) and the 3-acetamidopropyl (**4j**), were prepared from methyldopa and the corresponding alcohol with $SOCl_2$ in low yields.

Since the presence of a quarternary chiral center in (*S*)- (or L-) α-methyldopa precludes inversion or racemization during preparation of the esters in this series, the amino acid portion of these esters retains the *S* configuration. When the alcohol portion contains an additional chiral center, e.g., the α-succinimidoethyl (**4a**) and the α-pivaloyloxyethyl (**4t**) esters, two diastereomeric isomers are possible. In these cases, the pure diastereomers, **4u**, **4w**, and **4x**, arbitrarily designated α and β, were obtained either through fractional crystallization of the isomeric mixture or, in the case of **4a**, by removing the protecting group of the purified α and β isomers of **3**. The configuration of the second chiral center of **4u**, **4w**, and **4x** was not determined.

The required alkylating agents 3-chloromethyl-1-methylhydantoin (**6**) and *N*-chloromethylglutarimide were synthesized by hydroxymethylation of **5** or glutarimide with formaldehyde, followed by reaction with $SOCl_2$. Addition of HCl to *N*-propenyl- (**8a**) or *N*-vinyl- (**8b**) succinimides provided **9a** and **9b** in good yield. *N*-Propenylsuccinimide in turn was prepared by $Fe(CO)_5$ catalyzed isomerization of *N*-allylsuccinimide (**7**) by the procedure of Barolo and Rossi.[5] α-Chloroethyl pivalate was obtained by reaction of pivaloyl chloride with acetaldehyde in the presence of $ZnCl_2$[6].

Biological Results and Discussion. The relative antihypertensive potencies following oral administration to the SH rat of some of the more potent esters from the series are compared with methyldopa and its ethyl ester in Tables I and II. Except for the nicotinamidoethyl ester **4b**, all esters having a heteroatom separated from the carboxylate oxygen by two or more carbon atoms proved to be less active than methyldopa. Of those esters having a one carbon atom separation of heteroatoms, the pivaloyloxy and succinimidoalkyl derivatives, **4a** and **4s–x**, were found to be more potent than methyldopa. It is interesting to note that ring expansion of the succinimide group to glutarimide **4k**, conversion to the hydantoin **4m**, or lengthening the alkyl chain to α-ethyl, **4c**, led to a decrease in antihypertensive activity. On the basis of the antihypertensive data in Tables I and II, the crystalline esters **4u** and **4w** were selected for further pharmacological study.

The pivaloyloxyethyl ester **4u** was tested in SH rats at 6, 18, and 54 mg/kg ip and at 6, 18, 54, and 162 mg/kg po, with a minimum of six animals in each treatment group. Antihypertensive activity was observed at 18 mg/kg ip or po and higher doses, while no significant activity was seen at 6 mg/kg ip or po. The maximal antihypertensive effect was reached by either route at 2–8 h after treatment, with a duration of action exceeding 12 h and in some experiments even 24 h. The effect ranged from a 17 mmHg fall in mean arterial pressure at 18 mg/kg po to 56 mmHg at 162 mg/kg po.

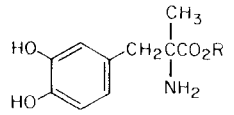
The succinimidoethyl ester **4w** was tested in SH rats at 9.5, 19, and 38 mg/kg ip and 4, 9.5, 12, 19, 36, and 38 mg/kg po, with six animals in each treatment group. In contrast to **4u**, this ester exhibited antihypertensive activity at all doses used. The maximal effect was usually observed at 2–4 h following ip and at 4–12 h following po administration. As with **4u**, the duration of action usually exceeded 12 h and in some experiments even 24 h. The antihypertensive effect of **4w** ranged from 7 mmHg at 4 mg/kg po to 30 mmHg at 38 mg/kg po.

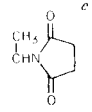
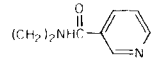
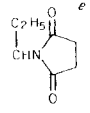
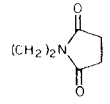
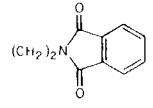
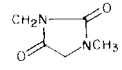
The duration of antihypertensive action of either **4u** or **4w** at the highest doses used was longer than that of methyldopa at 90 mg/kg po (maximal dose used in our experiments). At this dose, the duration of action of methyldopa exceeded 8 but not 12 h.

At doses considerably higher than those used in SH rats (50–240 mg/kg po), esters **4t** and **4w** also lowered systolic arterial pressure in conscious renal hypertensive African green monkeys. The antihypertensive effect in this species did not exceed 20 mmHg with either compound at any of the doses used.

Hydrolysis of the esters was studied at 37 °C over a wide range of pH values in order to explore the possibility that antihypertensive activity might correlate with the rate of ester hydrolysis. In these studies, liberated methyldopa was determined fluorometrically following reaction with an alkaline aqueous solution of *o*-phthaldehyde.[7] Solutions of esters capable of forming aldehydes upon hydrolysis,

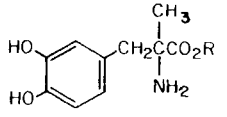
Table I. Methyldopa Esters, Chemical and SH Rat Antihypertensive Properties

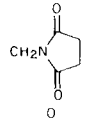
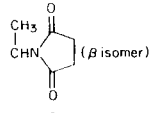
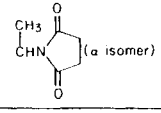


no.	R	dec point,[a] °C	method	alkylating agent R-X, X	yield,[b] %	formula	analyses	hydrolysis, $t_{1/2}$,[c] min	antihypertensive act., po, SH rat[d]
1	H (methyldopa)					$C_{10}H_{13}NO_4 \cdot 1.5H_2O$			++
4a	 [c]		A	Cl	38	$C_{16}H_{20}N_2O_6 \cdot HCl \cdot 0.5AcOH$	C, H, N		
		114	B	Cl	61	$C_{16}H_{20}N_2O_6 \cdot HCl \cdot 0.5EtOAc$[f]	C, H, N	300	+++
4b			C	Cl	65	$C_{18}H_{21}N_3O_5 \cdot 2HBr \cdot 2H_2O$	C, H, N, Br		+++
4c	 [e]	120	B	Cl	35	$C_{17}H_{22}N_2O_6 \cdot HCl \cdot EtOH$[f]	H, N; C[g]	360	++
4d		130	D	Br	28	$C_{16}H_{20}N_2O_6 \cdot HCl \cdot 0.25H_2O$	C, H, N	2000	++
4e		138–140	E	Br	33	$C_{20}H_{20}N_2O_6 \cdot HCl \cdot 0.25H_2O$	C, N; H, Cl[h]	1800	++
4f	$(CH_2)_2NHC(=O)CH_3$	125–126	F		15	$C_{14}H_{20}N_2O_5 \cdot HCl$	C, H, N	1700	++
4g	$(CH_2)_2NHC(=O)CF_3$		G	Cl	42	$C_{14}H_{17}F_3N_2O_5 \cdot HCl \cdot EtOH$[f]	C, H, N	1050	++
4h	$(CH_2)_2OC(=O)CH_3$	114–118	H	Cl	17	$C_{14}H_{17}NO_6$	C, H, N	1500	++
4i	$-CH_2CH_2-$	114	B	$Br(CH_2)_2Br$	40	$C_{22}H_{28}N_2O_8 \cdot 2HCl \cdot EtOAc$[f]	C, H, N	1700	++
4j	$(CH_2)_3NHC(=O)CH_3$	95–98	I		2.6	$C_{15}H_{22}N_2O_5 \cdot C_2H_2O_4$[i] $\cdot H_2O$	C, N; H[j]		++
4k		115	B	Cl	34	$C_{16}H_{20}N_2O_6 \cdot HCl \cdot 0.75EtOAc$[f]	C, H, N	330	+
4l		102	J	Cl	1.9	$C_{15}H_{19}N_3O_4 \cdot 2HCl \cdot 1.5H_2O$	C, H, N	390	+
4m		85	J	Cl	17	$C_{15}H_{19}N_3O_6 \cdot HCl \cdot 1.5H_2O \cdot 0.5EtOAc$	C, H, N	330	+
4n	$(CH_2)_2NHC(=O)C_6H_5$	85	J	Cl	20	$C_{19}H_{22}N_2O_5 \cdot 0.5C_2H_2O_4$[k] $\cdot H_2O$	C, H, N	2200	+
4o	$(CH_2)_2OCH_3$	90–92	H	OTs	16	$C_{13}H_{19}NO_5$	C, H, N		+
4p	$CH_2C_6H_5$		K	Cl	61	$C_{17}H_{19}NO_4$	C, H, N		+
4q	$(CH_2)_2OC_6H_5$	57–63	L	Br	50	$C_{18}H_{21}NO_5 \cdot HCl \cdot 0.5H_2O$	C, H, N	1700	0

[a] The decomposition point is not a reliable criterion of purity in this series. In some cases, the sample was too hygroscopic for decomposition point determination. [b] Yields calculated from 2b for methods B–E, G, H, J, and L, from methyldopa for methods A and K, and from the alcohol for methods F and I. [c] 37 °C, pH 7.4. See the Experimental Section for procedure. [d] All esters were tested at a molar equivalent dose to 40 mg/kg of methyldopa sesquihydrate. See the Experimental Section for procedure. +++ = over 40 mmHg decrease in blood pressure, ++ = 30–39 mmHg decrease, + = 20–29 mmHg decrease, 0 = less than 20 mmHg decrease. [e] Diastereomeric mixture. [f] Solvate determined by ^1H NMR. [g] C: calcd, 52.71; found, 53.62. [h] H: calcd, 5.09; found, 5.62. Cl: calcd, 8.33; found, 8.75. [i] Hydrogen oxalate. [j] H: calcd, 6.26; found, 6.85. [k] Oxalate.

Table II. Methyldopa Esters, Chemical and SH Rat Antihypertensive Properties



no.	R	dec point,[a] °C	method	alkylating agent R–X, X	yield,[b] %	formula	analyses	hydrolysis, $t_{1/2}$,[c] min	rel antihypertensive potency,[d] po, SH rat (95% C.L.)
1	H (methyldopa)					$C_{10}H_{13}NO_4 \cdot 1.5H_2O$			1
4r	C_2H_5		A	Cl	37	$C_{16}H_{23}NO_6 \cdot HCl \cdot 0.5AcOH$[e]	C, H, N	7700	1.2 (0.9–1.8)[i]
4s	$CH_2O_2CC(CH_3)_3$	95–103	D	Cl	23	$C_{16}H_{23}NO_6 \cdot HCl$	C, H, N	<350	1.9 (1.2–3.3)[j]
4t	$CHO_2CC(CH_3)_3$[f]	125–130	M	Cl	48	$C_{17}H_{25}NO_6 \cdot HCl \cdot H_2O$	C, H, N, Cl	320	2.3 (1.3–4.0)[j]
4u	$CHO_2CC(CH_3)_3$ (α isomer)	92–96	N		69[g]	$C_{17}H_{25}NO_6 \cdot HCl \cdot 2H_2O$	C, H, N, Cl		2.7 (1.7–4.4)[j]
4v		120	D	Br	46	$C_{15}H_{18}N_2O_2 \cdot HCl \cdot H_2O$	C, H, N	170	3.4 (2.4–5.1)[j]
			O	Br	37	$C_{15}H_{18}N_2O \cdot HBr \cdot 0.5H_2O \cdot {}^1/_3Me_2SO$[e]	C, H, N		
4w		130.5–131.5	P	Cl	27	$C_{16}H_{20}N_2O_6 \cdot HCl \cdot 2H_2O$	C, H, N	360	3.2 (1.8–5.8)[j]
4x			Q	Cl	38	$C_{16}H_{20}N_2O_6 \cdot HCl \cdot H_2O$	H, N; C[h]		4.4 (3.0–6.6)[j]

[a] The decomposition point is not a reliable criterion of purity in this series. In some cases, the sample was too hygroscopic for decomposition point determination. [b] Yields calculated from 2b for methods D, M, P, and Q and from methyldopa sesquihydrate for methods A and O. [c] 37 °C, pH 7.4. See the Experimental Section for procedure. [d] Calculated from ED_{50} of methyldopa sesquihydrate (mmol/kg) divided by ED_{50} of ester base (mmol/kg). See the Experimental Section for assay protocol. Relative potencies calculated by the standard parallel assay method described by Finney.[9] [e] Solvate determined by ^1H NMR. [f] Diastereomeric mixture. [g] Yield of α isomer by crystallization from the α- and β-isomer mixture 4t. [h] C: calcd, 49.17; found, 48.57. [i] Not statistically significant ($p = 0.05$) compared to methyldopa sesquihydrate. [j] Statistically significant ($p \leq 0.05$) compared to methyldopa sesquihydrate.

i.e., those esters with a one carbon atom separation of heteroatoms, also contained aldehyde-trapping agents such as dimedone or L-cysteine in order to avoid formation of tetrahydroisoquinolines.

Although the esters prepared in this series were relatively stable under acidic conditions, they proved to be considerably more labile than the ethyl ester, $t_{1/2}$ = 7700 min, at pH 7.4. The esters could be divided into two distinct groups by their hydrolysis times at pH 7.4. Those derivatives, with one carbon atom separating the heteroatoms, uniformly formed methyldopa at a significantly faster rate than esters having more than one carbon atom separating the heteroatoms. All of the esters found to be more potent antihypertensive agents than methyldopa in the SH rat were hydrolyzed to the amino acid at a relatively fast rate with $t_{1/2} \leq 360$ min at pH 7.4 and 37 °C. However, rate of chemical hydrolysis to methyldopa cannot be the sole determinant of antihypertensive potency, since other esters, **4k** and **4m**, which were hydrolyzed to methyldopa with $t_{1/2}$ = 330 min, were less potent antihypertensives than methyldopa in the SH rat.

Antihypertensive activity in the SH rat apparently does not correlate directly with the rate of chemical hydrolysis for this series of esters. Either the less potent esters are poorly absorbed compared to the more active compounds or they are poorer substrates for enzymatic hydrolysis.

Vickers and co-workers[8] studied the absorption and metabolism of labeled esters **4u** and **4w** in the SH rat and established that both esters were better absorbed and indeed yielded higher plasma and brain levels of the amino acid when compared with equivalent doses of methyldopa. However, ensuing clinical trials with **4u** and **4w** demonstrated that although both esters possess antihypertensive activity in man, the relative potency of these progenitors appeared to differ from that observed in SH rats.[8] While both **4u** and **4w** were approximately three times more potent than methyldopa (on a molar basis) in lowering blood pressure in the SH rat, in man the pivaloyloxyethyl ester **4u** appeared to be more potent than the succinimidoethyl ester **4w**. In addition, the succinimidoethyl ester **4w** did not produce the anticipated threefold increase in antihypertensive potency over methyldopa.

Experimental Section

All melting points were obtained on a Thomas-Hoover Unimelt capillary melting point apparatus using open capillaries and are uncorrected. Analytical results are indicated by atom symbols and are within ±0.4% of theoretical values unless otherwise indicated. ^{1}H NMR spectra were recorded for all intermediates and final products on a Varian T-60 spectrophotometer in either $CDCl_3$, Me_2SO-d_6, or D_2O and were consistent with assigned structures. TLC's were performed on fluorescent silica gel plates and spots detected by UV or exposure to I_2 vapor. Optical rotations were determined with a Perkin-Elmer polarimeter, Model 141. Fluorometric assays were performed with an Aminco-Bowman spectrophotofluorometer.

(*S*)-α-Amino-2,2-diphenyl-α-methyl-1,3-benzodioxole-5-propanoic Acid Hydrochloride (2a). A mixture of (*S*)-3-hydroxy-α-methyltyrosine (19.3 g, 0.0777 mol) and dichlorodiphenylmethane (37 g, 0.156 mol) was immersed with slow stirring into a preheated oil bath at 190 °C. After reaction had started, as evidenced by vigorous gas evolution, the reaction mixture was stirred rapidly for 6 min at 190 °C, removed from the hot oil bath, and allowed to cool to 25–30 °C. The crude product from 12 such runs was combined, slurried with Et_2O (3 L), filtered, washed again with Et_2O (2 L), and dried at 30 °C (50 mm). Recrystallization from EtOH–EtOAc gave 255 g (66.4%) of product, mp 267–268 °C dec. Anal. ($C_{23}H_{21}NO_4$·HCl) C, H, N.

(*S*)-2,2-Diphenyl-α-methyl-α-[[(phenylmethoxy)carbonyl]amino]-1,3-benzodioxole-5-propanoic Acid (2b). A mixture of **2a** (175 g, 0.425 mol), Me_2CO (1750 mL), and H_2O (1750 mL) was stirred under N_2 at a temperature below 10 °C while the pH was adjusted to 12.0 by the slow addition of 10% NaOH. Carbobenzyloxy chloride (93 g, 0.545 mol) was added dropwise over 5–7 min to the reaction mixture at 20–30 °C, accompanied by the simultaneous addition of sufficient 10% NaOH solution to maintain a pH of 12.0–12.2. After addition of the carbobenzyloxy chloride was complete, the reaction mixture was stirred at 25–30 °C for an additional 3 h. Most of the Me_2CO was then removed under reduced pressure at 25–35 °C to precipitate the sodium salt of the desired *N*-carbobenzyloxy derivative. The sodium salt was extracted into EtOAc (1.5 L), washed with 5% NaOH solution (200 mL) and saturated NaCl solution (200 mL), and dried ($MgSO_4$). After adding 17.5 g of decolorizing carbon and filtering through a $MgSO_4$ pad, solvents were removed under reduced pressure at 25–35 °C. The residue was slurried two times with 20% Et_2O–80% hexane solution (1 L) and filtered to give the sodium salt of the desired *N*-carbobenzyloxy derivative. This sodium salt was dissolved in EtOAc (1.5 L), cooled to 10 °C, and acidified to pH 2 with 6 N HCl. The EtOAc extract was washed with saturated NaCl solution (200 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure at 25–35 °C. The *N*-carbobenzyloxy derivative was dried further at 25–30 °C and 0.2–0.3 mm to give 169 g (78.0%) of **2b** as a foam which resisted all attempts at crystallization.

Preparation of Methyldopa Esters. Method A. 1-(2,5-Dioxo-1-pyrrolidinyl)ethyl (*S*)-3-Hydroxy-α-methyltyrosinate Hydrochloride AcOH Solvate, α- and β-Isomeric Mixture (4a). A solution of (*S*)-3-hydroxy-α-methyltyrosine sesquihydrate (0.95 g, 4.0 mmol) and *N*-(α-chloroethyl)succinimide (0.65 g, 4.0 mmol) in Me_2SO (5 mL) was stirred at 20–25 °C for 23 h. The solution was diluted with distilled H_2O (10 mL) and passed through a column containing 5 g of weakly basic anion-exchange resin IR-45 on the basic cycle. After elution with H_2O, the fractions giving a positive $FeCl_3$ test were combined and added to a column of 3 g of a weakly acidic cation-exchange resin CG-50 on the acid cycle. Unreacted amino acid was eluted with distilled H_2O until a negative $FeCl_3$ test was obtained. The ester was then eluted with 1 N HOAc. The ester fraction, 55 mL (pH 3.2), was treated with 1 N HCl to pH 2.0 and lyophilized at 0.1–0.3 mm for 20 h to give 0.60 g (38%) of **4a** hydrochloride as the AcOH solvate.

Method B. 1-(2,5-Dioxo-1-pyrrolidinyl)propyl (*S*)-2,2-Diphenyl-α-methyl-α-[[(phenylmethoxy)carbonyl]amino]-1,3-benzodioxole-5-propanoate (3c). A solution of **2b** (10.2 g, 0.020 mol), Et_3N (2.1 g, 0.021 mol), and 1-chloro-1-succinimidopropane (3.51 g, 0.020 mol) in DMF (20 mL) was heated at 90 °C for 10 h and then poured into H_2O (200 mL). The product was extracted with three 100-mL portions of Et_2O and washed with 5% NaOH (50 mL), H_2O (50 mL), and saturated NaCl solution (50 mL). After drying ($MgSO_4$) and filtering, solvents were removed under reduced pressure to give 8.6 g (68%) of **3c**, homogeneous on TLC ($CHCl_3$).

1-(2,5-Dioxo-1-pyrrolidinyl)propyl (*S*)-3-Hydroxy-α-methyltyrosinate Hydrochloride EtOH Solvate (4c). A solution of **3c** (8.6 g, 0.014 mol) in a 25% EtOH–75% EtOAc solution (120 mL) was hydrogenated with 10% Pd/C catalyst (4 g) at an initial pressure of 40 psi for 18 h until H_2 uptake ceased. After removing catalyst by filtration, solvents were removed under reduced pressure at 30–40 °C. The residue was dissolved in 10% EtOH–90% EtOAc and stirred with saturated Na_2CO_3 solution (5 mL) and excess solid Na_2CO_3 (5 g) for 2 min. Anhydrous $MgSO_4$ (10 g) was added, the mixture filtered, and the filtrate acidified with 0.6 N EtOH–HCl solution (2 mL). The solution was concentrated to dryness under reduced pressure, EtOAc (100 mL) added, and the mixture concentrated again to dryness under reduced pressure. EtOAc (100 mL) was added; and after stirring at 25 °C for 1 h, the product was removed by filtration and dried under reduced pressure to give 3.0 g (51.0%) of **4c** hydrochloride as an EtOH solvate.

Method C. 2-[(3-Pyridinylcarbonyl)amino]ethyl (*S*)-2,2-Diphenyl-α-methyl-α-[[(phenylmethoxy)carbonyl]-amino]-1,3-benzodioxole-5-propanoate (3b). A solution of **2b** (5.84 g, 0.015 mol), Et_3N (1.52 g, 0.015 mol), and *N*-(2-chloroethyl)nicotinamide (2.77 g, 0.015 mol) in dry DMF (20 mL) was stirred under N_2 at 95 °C for 20 h. The cooled reaction mixture was poured into ice H_2O (200 mL) and the product extracted into three 175-mL portions of EtOAc. The combined extracts were

washed with a saturated $NaHCO_3$ solution (100 mL) and H_2O (100 mL) and dried ($MgSO_4$). After filtering, solvents were removed under reduced pressure to give 6.28 g (85%) of **3b**, homogeneous on TLC (20% MeOH–80% C_6H_6).

2-[(3-Pyridinylcarbonyl)amino]ethyl (*S*)-3-Hydroxy-α-methyltyrosinate Dihydrobromide Dihydrate (4b). A mixture of **3b** (1.0 g, 2.0 mmol) and a 30–32% solution of anhydrous HBr in HOAc (10 mL) was allowed to stand at 20–25 °C for 30 min until gas evolution was complete. The homogeneous solution was concentrated under reduced pressure at 20–25 °C and the residue stirred with Et_2O (50 mL) for 3 days. The nearly white solid was collected, washed with anhydrous Et_2O (50 mL), and dried at 0.1–0.3 mm to give 800 mg (77%) of **4b** dihydrobromide dihydrate.

Method D. 2-(2,5-Dioxo-1-pyrrolidinyl)ethyl (*S*)-3-Hydroxy-α-methyltyrosinate Hydrochloride Hydrate (4d). A suspension of the protected ester (2.5 g, 3.94 mmol), prepared from **2b** and *N*-(2-bromoethyl)succinimide by method B, in MeOH (75 mL), EtOH (75 mL), and 7.6 N EtOH–HCl solution (3 mL) was hydrogenated with 10% Pd/C catalyst (1.2 g) at an initial pressure of 20 psi for 20 h. After removing catalyst by filtration, solvents were removed under reduced pressure, and the residue was stirred with C_6H_6 (25 mL) and then EtOAc (25 mL). The insoluble material was treated with 10% EtOH–90% EtOAc (100 mL), saturated Na_2CO_3 solution (5 mL), and solid Na_2CO_3 (5 g). The organic extract was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. EtOH–HCl solution (9.6 N, 1 mL) was added. Removal of all solvents under reduced pressure gave 0.5 g (33%) of **4d** hydrochloride hydrate.

Method E. 2-(1,3-Dihydro-1,3-dioxo-2*H*-isoindol-2-yl)ethyl (*S*)-2,2-Diphenyl-α-methyl-α-[[(phenylmethoxy)carbonyl]amino]-1,3-benzodioxole-5-propanoate (3e). A solution of **2b** (10.18 g, 0.020 mol), Et_3N (2.12 g, 0.021 mol), and *N*-(2-bromoethyl)phthalimide (5.08 g, 0.020 mol) in DMF (30 mL) was stirred under N_2 at 105–110 °C overnight and then poured into ice H_2O (600 mL). The product was extracted into three 100-mL portions of Et_2O and washed with H_2O (50 mL). The Et_2O extract was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a gummy solid. Chromatography over silica gel and elution with $CHCl_3$ afforded 10.88 g (80%) of **3e**, homogeneous on TLC ($CHCl_3$).

2-(1,3-Dihydro-1,3-2*H*-isoindol-2-yl)ethyl (*S*)-3-Hydroxy-α-methyltyrosinate Hydrochloride Hydrate (4e). A solution of **3e** (10.88 g, 0.0159 mol) in EtOAc (125 mL) was hydrogenated with a 10% Pd/C catalyst (6 g) at an initial pressure of 31 psi for 5 h until H_2 uptake ceased. After removing catalyst by filtration and removing solvents under reduced pressure, the residue was dissolved in absolute EtOH (150 mL) containing 5.15 N EtOH–HCl solution (4 mL) and hydrogenated with a 10% Pd/C catalyst (4.3 g) at 27–38 psi for 5 days. Additional amounts of catalyst (4.3 g) were added during this time. After removing catalyst by filtration and concentrating under reduced pressure, the residue was washed with petroleum ether (100 mL) and then precipitated three times from EtOH–Et_2O to give 2.80 g (41.8%) of **4e** hydrochloride hydrate, mp 138–140 °C dec.

Method F. 2-(Acetylamino)ethyl (*S*)-3-Hydroxy-α-methyltyrosinate Hydrochloride (4f). A slurry of (*S*)-3-hydroxy-α-methyltyrosine hydrochloride EtOH solvate (88.3 g, 0.30 mol) (from concentration of an EtOH solution of the hydrochloride salt under reduced pressure) and *N*-acetylethanolamine (146.4 g, 1.42 mol) under N_2 was warmed to 104–108 °C. Thionyl chloride (84.8 g, 0.713 mol) was added over 15 min with stirring. The reaction mixture foamed vigorously during the addition. After addition was complete, the reaction mixture was stirred at 104–108 °C for 18 h. Additional $SOCl_2$ (42.4 g, 0.357 mol), was added over 7 min. The reaction mixture was allowed to stir at 104–108 °C for another 3.5 h, then cooled to 30 °C and concentrated under reduced pressure to yield a viscous oil. This oil was slurried with $CHCl_3$ (100 mL) and the $CHCl_3$ removed under reduced pressure. This was repeated three more times, and then the oil was washed with C_6H_6 (100 mL) which was decanted. The residue was dissolved in *i*-PrOH (700 mL) and added to Et_2O (6 L). The precipitate which formed was washed with Et_2O (500 mL) and shaken with 10% EtOH–90% EtOAc (6 L), saturated Na_2CO_3 solution (150 mL), and Na_2CO_3 (100 g). The organic extract was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give the free base of the acetamidoethyl ester. This base was treated with fumaric acid (15 g) in *i*-PrOH (300 mL) and the fumarate salt precipitated by adding sufficient Et_2O. The fumarate salt was precipitated once more from *i*-PrOH by adding sufficient Et_2O and then converted back to the free base as before by shaking with 10% EtOH–90% EtOAc (200 mL), saturated Na_2CO_3 solution (20 mL), and solid Na_2CO_3 (20 g). The free base was converted to the HCl salt by dissolving in absolute EtOH (100 mL), adding 9.6 N EtOH–HCl (10 mL), and precipitated by addition to Et_2O (1 L). After three precipitations from EtOH–Et_2O as carried out above, 15.1 g (15%) of the HCl salt of **4f** was obtained.

Method G. 2-(Trifluoroacetylamino)ethyl (*S*)-3-Hydroxy-α-methyltyrosinate Hydrochloride EtOH Solvate (4g). A solution of 2-(trifluoroacetylamino)ethyl (*S*)-2,2-diphenyl-α-methyl-α-[[(phenylmethoxy)carbonyl]amino]-1,3-benzodioxole-5-propanoate (2.0 g, 3.1 mmol), prepared from **2b** and *N*-(2-chloroethyl)trifluoroacetamide by method B, in absolute EtOH (125 mL) and 10% Pd/C catalyst (1.0 g) was hydrogenated at room temperature and an initial pressure of 36 psi for 4 h and 40 min until H_2 uptake was complete. Catalyst was removed by filtration under N_2 through a diatomaceous earth filter pad and the filtrate concentrated under reduced pressure at a temperature of 20–30 °C. The residue was redissolved in absolute EtOH (25 mL), converted to the hydrochloride salt by addition of 7.6 N EtOH–HCl solution (2 mL), and then concentrated under reduced pressure. The residue was precipitated twice by dissolving in EtOH and adding sufficient Et_2O to precipitate the product to give 800 mg (66.6%) of **4g** hydrochloride as an EtOH solvate.

Method H. 2-(Acetyloxy)ethyl (*S*)-2,2-diphenyl-α-methyl-α-[[(phenylmethoxy)carbonyl]amino]-1,3-benzodioxole-5-propanoate (3h) was prepared from **2b** and 2-chloroethyl acetate by method E. The protected ester **3h** was eluted from the silica gel column with 5% MeOH–95% $CHCl_3$.

2-(Acetyloxy)ethyl (*S*)-3-Hydroxy-α-methyltyrosinate (4h). A solution of **3h** (5.60 g, 9.4 mmol) in absolute EtOH (100 mL) was hydrogenated with a 10% Pd/C catalyst (2.8 g) at an initial pressure of 37 psi for 24 h until H_2 uptake was complete. After removing catalyst by filtration and removing solvents under reduced pressure, the residue was washed with petroleum ether (100 mL) and dissolved in 10% EtOH–90% EtOAc (124 mL). Na_2CO_3 (6.2 g) and a saturated Na_2CO_3 solution (4 mL) solution were added and stirred for 20 min. The mixture was filtered, dried ($MgSO_4$), filtered, and concentrated under pressure. The residue was chromatographed over silica gel and product eluted with 20% MeOH–80% C_6H_6. Recrystallization from EtOAc–cyclohexane afforded 1.01 g (36%) of **4h**, mp 114–118 °C dec.

Method I. 3-(Acetylamino)propyl (*S*)-3-Hydroxy-α-methyltyrosinate Hydrogen Oxalate Hydrate (4j). $SOCl_2$ (275 mL) was added to (*S*)-3-hydroxy-α-methyltyrosine sesquihydrate (250 g) at 25 °C and the mixture heated on the steam bath. After heating for 2 h, the thick reaction mixture was diluted with a mixture of DMF (7.5 mL) and C_6H_6 (25 mL) and stirred on the steam bath until gas evolution ceased. C_6H_6 (100 mL) was added and the crude sulfurous acid ester removed by filtration, washed with C_6H_6 (100 mL), $CHCl_3$ (100 mL), and Et_2O (100 mL), and dried under reduced pressure to give 280 g of the sulfurous acid ester intermediate, mp 199 °C dec.

A mixture of the crude sulfurous acid ester intermediate (13.7 g), *N*-acetylpropanolamine (24.98 g, 0.212 mol), and anhydrous DMF (2 g) was stirred on the steam bath for 20 h and cooled. The reaction mixture was washed with six 200-mL portions of Et_2O and four 200-mL portions of CH_2Cl_2 and dried under reduced pressure. The semisolid material remaining was stirred with 20% EtOH–80% EtOAc (200 mL), saturated Na_2CO_3 solution (20 mL), and solid Na_2CO_3 (20 g). The organic extract was dried ($MgSO_4$) and filtered, and the filtrate was added to a solution of oxalic acid (3.2 g) in EtOH (50 mL). Addition of Et_2O (500 mL) provided 2.32 g (2.6%) of product.

Method J. The same procedure as method B was followed, except that the catalytic reduction was carried out in absolute EtOH.

Method K. Benzyl (*S*)-3-Hydroxy-α-methyltyrosinate (4p). A mixture of (*S*)-3-hydroxy-α-methyltyrosine sesquihydrate (2.38 g, 0.010 mol), benzyl chloride (1.27 g, 0.010 mol), and Me_2SO (10 mL) was stirred at 65 °C for 7 h and then cooled. After removing most of the Me_2SO by washing with Et_2O, saturated

Na_2CO_3 solution was added and the ester extracted into EtOAc. The EtOAc extract was washed several times with H_2O, dried ($MgSO_4$), filtered, and concentrated to give the benzyl ester as a hygroscopic foam, 1.85 g (61%).

Method L. The same procedure as method H was followed, except that the ester was eluted from the silica gel column with 5% MeOH–95% C_6H_6 and converted to the HCl salt with EtOH–HCl solution in 1:1 $CHCl_3$–MeOH.

Method M. 1-(2,2-Dimethyl-1-oxopropoxy)ethyl (*S*)-2,2-Diphenyl-α-methyl-α-[[(phenylmethoxy)carbonyl]amino]-1,3-benzodioxole-5-propanoate, α and β Isomers (3t). To a stirred solution of **2b** (10.2 g, 0.020 mol) in dry DMF (23 mL) was added Et_3N (2.02 g, 0.020 mol) followed by α-chloroethyl pivalate (3.3 g, 0.020 mol). After stirring at 90 °C for 6 h, the reaction mixture was poured into ice H_2O (230 mL) and the product extracted into Et_2O solution, washed with an aqueous saturated NaCl solution, and dried ($MgSO_4$). After filtering, solvent was removed under reduced pressure and the residue dried under high vacuum to give 9.5 g (74.5%) of a gummy crude product.

1-(2,2-Dimethyl-1-oxopropoxy)ethyl (*S*)-3-Hydroxy-α-methyltyrosinate Hydrochloride Hydrate, α and β Isomers (4t). A solution of **3t** (9.27 g, 14.77 mmol) in absolute EtOH (100 mL) was hydrogenated with 10% Pd/C catalyst (4 g) on a Parr shaker at 35 psi and room temperature. H_2 uptake ceased after 5.5 h. EtOH–HCl (1.52 mL of 10.71 N) was added and the catalyst removed by filtration. The filtrate was concentrated to dryness in vacuo (not over 30 °C) and the residue dissolved in EtOAc (10 mL). The EtOAc solution was added slowly with good stirring to hexane (200 mL) at room temperature. After stirring for 0.5 h, the supernatant was removed by decantation and the gummy residue washed two times with hexane. The residue was then dissolved in EtOAc (200 mL) and Na_2CO_3 (10 g) added, followed by saturated Na_2CO_3 solution (5 mL). The mixture was stirred for 2 min, and anhydrous $MgSO_4$ and decolorizing carbon were added. The mixture was filtered through a pad of $MgSO_4$. EtOH–HCl (1.52 mL of 10.71 N) was added to the filtrate and the solvent removed in a vacuum under 30 °C. Final drying was done at 60 °C, high vacuum, to give a foam which was dissolved in water (10 mL/g) and immediately filtered through diatomaceous earth. The filtrate was quickly frozen and lyophilized to give 3.57 g (64%) of product: ^1H NMR (D_2O) δ 1.13 [9 H, s, $C(CH_3)_3$], 1.47–1.67 (6 H, four-line multiplet, CCH_3), 3.07 (2 H, br q, CH_2), 6.57–7.05 (4 H, m, CH and aromatic).

Method N. 1-(2,2-Dimethyl-1-oxopropoxy)ethyl (*S*)-3-Hydroxy-α-methyltyrosinate Hydrochloride Dihydrate, α Isomer (4u). A solution of the hydrochloride hydrate of **4t** (10.0 g) in H_2O (20 mL) was diluted with concentrated HCl (20 mL) and allowed to stand at 20–25 °C for 3 h. The solid was collected, washed with cold 6 N HCl (10 mL) and three 20-mL portions of Et_2O, and dried to give 3.76 g (69%) of the α isomer **4u** as the hydrochloride dihydrate: mp 92–96 °C; $[\alpha]^{24}_D$ –0.5° (*c* 1.5, MeOH); ^1H NMR (D_2O) δ 1.12 [9 H, s, $C(CH_3)_3$], 1.25 (3 H, d, J = 5 Hz, CH_3), 1.62 (3 H, s, CH_3), 3.05 (2 H, q, CH_2), 6.48–7.02 (4 H, m, CH and aromatic).

Method O. (2,5-Dioxo-1-pyrrolidinyl)methyl (*S*)-3-Hydroxy-α-methyltyrosinate Hydrobromide Hemihydrate Me_2SO Solvate (4v). A solution of (*S*)-3-hydroxy-α-methyltyrosine sesquihydrate (1.20 g, 5.05 mmol) and *N*-bromomethylsuccinimide (0.96 g, 5.0 mmol) in Me_2SO (2 mL) was stirred at 20–25 °C for 20–24 h. Me_2SO was removed by stirring with Et_2O (20 mL) for several minutes and then decanting off the Et_2O layer. This extraction process was carried out three times. The residue was dissolved in absolute EtOH (25 mL) and the product precipitated by the addition of excess Et_2O. This precipitation process was repeated two more times. The precipitated product was extracted into Me_2CO (50 mL) and filtered from a small amount of insoluble oil, and the Me_2CO was removed under reduced pressure (15–20 mmol) at 30–40 °C. The residue was dissolved in distilled H_2O (10 mL) and lyophilized at 0.1–0.2 mm to give 0.80 g (37%) of **4v** as the hydrobromide hemihydrate Me_2SO solvate.

Method P. 1-(2,5-Dioxo-1-pyrrolidinyl)ethyl (*S*)-2,2-Diphenyl-α-methyl-α-[[(phenylmethoxy)carbonyl]amino]-1,3-benzodioxole-5-propanoate, α and β Isomers. A mixture of **2b** (30.66 g, 0.060 mol), *N*-(1-chloroethyl)succinimide (9.70 g, 0.06 mol), Et_3N (6.07 g, 0.070 mol), and dry DMF (75 mL) was stirred at 95 °C for 19 h. The reaction mixture was poured into H_2O (750 mL) and the product extracted into three 500-mL portions of EtOAc. The combined organic extracts were washed with three 300-mL portions of 5% NaOH solution and then three times with saturated NaCl solution and dried ($MgSO_4$). After filtering, the solution was treated with charcoal and filtered, and the solvent was evaporated under reduced pressure below 35 °C to give 37.90 g (99%) of ester as a mixture of diastereomeric isomers (α and β).

Separation of α and β Isomers of 1-(2,5-Dioxo-1-pyrrolidinyl)ethyl (*S*)-2,2-Diphenyl-α-methyl-α-[[(phenylmethoxy)carbonyl]amino]-1,3-benzodioxole-5-propanoate. The mixture of diastereomeric isomers (150.5 g) was dissolved in a boiling mixture of C_6H_6 (1200 mL) and absolute MeOH (100 mL) and filtered, and the filtrate was concentrated to a volume of approximately 700 mL. Absolute MeOH (100 mL) was added to the solution, which then was diluted to cloudiness with hexane (100 mL), seeded, and scratched to induce crystallization. The mixture was cooled at 5 °C for about 16 h and the crude, crystalline α isomer was collected, washed by suspension in a 50:50 mixture of C_6H_6 and hexane (200 mL), and dried at 70 °C to give 68.1 g, mp 185.5–191 °C. Two additional recrystallizations afforded an analytical sample, mp 199.5–201.5 °C. Anal. ($C_{37}H_{34}N_2O_8$) C, H, N.

The combined mother liquors and washings from the α isomer were evaporated to dryness under reduced pressure at 60 °C to give 79.3 g of the β isomer as a very viscous oil.

1-(2,5-Dioxo-1-pyrrolidinyl)ethyl (*S*)-3-Hydroxy-α-methyltyrosinate Hydrochloride Dihydrate, β Isomer (4w). A solution of the β isomer of the protected ester **3w** (10.0 g, 0.016 mol) in a 25% absolute EtOH–75% EtOAc solution (140 mL) was hydrogenated with 10% Pd/C catalyst (4.2 g) at an initial pressure of 40 psi and room temperature for 20 h until H_2 uptake was complete. The catalyst was filtered under N_2; the filtrate was acidified with 9.4 N EtOH–HCl (2.0 mL) and evaporated to dryness under reduced pressure below 40 °C. The amorphous solid residue was dissolved in warm 95% EtOH (50 mL) and filtered, and the filtrate was diluted to incipient cloudiness with anhydrous Et_2O (68 mL), seeded, and scratched to induce crystallization. The product was collected and stirred in anhydrous Et_2O (200 mL) to remove any diphenylmethane. After 1 h the solid was collected and dried at 70 °C overnight to give 3.7 g of product, mp 123–126 °C dec. An analytical sample, 3.36 g (51%), mp 130.5–131.5 °C dec, $[\alpha]^{24}_D$ +33.46° (*c* 1.5, MeOH), was obtained after one more recrystallization from 95% EtOH: ^1H NMR (Me_2SO-d_6) δ 1.43 (3 H, s, CH_3), 1.63 (3 H, d, J = 3.5 Hz, CH_3), 2.63 (4 H, s, CH_2CH_2), 2.97 (2 H, br s, CH_2), 3.42 (4 H, br s, D_2O exchangeable), 6.23–7.0 (4 H, m, aromatic CH), 8.33–9.33 (4 H, br m, D_2O exchangeable).

Method Q. 1-(2,5-Dioxo-1-pyrrolidinyl)ethyl (*S*)-3-Hydroxy-α-methyltyrosinate Hydrochloride Hydrate, α Isomer (4x). The α isomer of the protected ester **3x** (3 g, 4.7 mmol) from method P was suspended in 25% EtOH–75% EtOAc (42 mL) and the mixture hydrogenated at 40 psi and room temperature for 2 h with 10% Pd/C (1.3 g) as catalyst. After adding 8.0 N EtOH–HCl (1.0 mL), the hydrogenation mixture was filtered through diatomaceous earth and the filtrate concentrated under reduced pressure. The residue was stirred with Et_2O (200 mL), dissolved in H_2O (30 mL), and extracted with three 30-mL portions of Et_2O. Lyophilization of the aqueous layer afforded 1.56 g (85%) of the α isomer.

Intermediate Alkylating Agents. 1-(1-Chloropropyl)-2,5-pyrrolidinedione (9a). Anhydrous HCl was bubbled through a mixture of *N*-propenylsuccinimide (10 g, 0.072 mol), 200 mL of CCl_4, and stannic chloride (1.04 g) for 6 h. The solution was allowed to stand at room temperature for 10 days, the solution being saturated again with HCl gas after 3 and 4 days. Solvents were removed under reduced pressure at 30–40 °C to give **9a** as a yellow oil.

1-Hydroxymethyl-2,6-piperidinedione. A mixture of glutarimide (28.3 g, 0.25 mol) and 37% formalin solution (25 mL) was stirred on the steam bath for 4 h. After adding C_6H_6 (150 mL) and azeotroping off H_2O, the solution was concentrated to dryness. Recrystallization from C_6H_6 gave first unreacted glutarimide and then the desired crude hydroxymethylglutarimide.

Further recrystallization from C_6H_6–hexane afforded 9.2 g (26%) of *N*-hydroxymethylglutarimide: mp 55–60 °C; ^{1}H NMR ($CDCl_3$) δ 1.95 (2 H, quintet, CH_2), 2.58 (4 H, unsym t, CH_2), 3.95 (1 H, t, J = 8 Hz, D_2O exchangeable, OH), 5.22 [2 H, d, J = 8 Hz (s in D_2O), CH_2O].

1-Chloromethyl-2,6-piperidinedione. Thionyl chloride (8.35 g, 0.070 mol) was added slowly to a solution of *N*-hydroxymethylglutarimide (9.0 g, 0.063 mol) in C_6H_6 (50 mL) at 40 °C. After addition was complete, the solution was stirred at reflux for 1.5 h and then at room temperature for an additional 1.5 h. C_6H_6 was removed under reduced pressure at 30–40 °C and the residue distilled to give 5.4 g (53%) of *N*-chloromethylglutarimide: bp 97–100 °C (0.1 mm); ^{1}H NMR ($CDCl_3$) δ 1.93 (2 H, m, CH_2), 2.67 (4 H, m, CH_2), 5.3 (2 H, s, CH_2Cl).

3-Hydroxymethyl-1-methyl-2,4-imidazolinedione. A mixture of 1-methyl-2,4-imidazoledione (25 g, 0.219 mol) and 37% formalin solution (25 mL) was stirred on the steam bath for 6 h. After adding C_6H_6 and azeotroping, solvent was removed under reduced pressure. The residue was recrystallized from C_6H_6 to give 25 g (70%) of the hydroxymethyl derivative, mp 82–85 °C.

3-Chloromethyl-1-methyl-2,4-imidazolinedione (6). Thionyl chloride (30 mL) was added slowly over 20 min to a well-stirred mixture of 3-hydroxymethyl-1-methyl-2,4-imidazolinedione (25 g, 0.173 mol) and C_6H_6 (160 mL) at reflux. After stirring at reflux for 2 h, the reaction mixture was concentrated to dryness under reduced pressure, C_6H_6 (70 mL) was added, and the solution was concentrated again to dryness. After repeating this process one more time with C_6H_6 (70 mL), the residue was extracted with three 100-mL portions of CCl_4. Removal of solvents under reduced pressure gave 15.7 g (55.7%) of **6**.

1-Chloroethyl 2,2-Dimethylpropanoate.[6] $ZnCl_2$ (400 mg) was fused at 0.2–0.5 mm and cooled to 25–30 °C under N_2. Pivaloyl chloride (48 g, 0.40 mol) was added to the fused $ZnCl_2$, followed by acetaldehyde (19.2 g, 0.44 mol). During addition of the acetaldehyde, which was done as rapidly as possible, the reaction mixture was stirred and cooled to prevent loss of acetaldehyde due to the exothermic nature of the reaction. After heating at reflux for 1 h, distillation gave 36 g (55%) of ester: bp 32–34 °C (4 mm); ^{1}H NMR ($CDCl_3$) δ 1.53 [9 H, s, $C(CH_3)_3$], 1.77 (3 H, d, J = 5 Hz, CH_3), 6.55 (1 H, q, J = 6 Hz, CH).

1-(1-Chloroethyl)-2,5-pyrrolidinedione (9b). *N*-Vinylsuccinimide (50.0 g, 0.40 mol) was dissolved in CCl_4 (1 L), $SnCl_2$ (5.20 g, 0.020 mol) added, and the mixture stirred while saturating with HCl gas for 6 h at 20–30 °C. After 24 h, the mixture was resaturated with HCl for 1.5 h. At the end of 48 h, the solution was decanted and the gummy residue washed with ten 100-mL portions of CCl_4. The combined extracts were slurried with 10 g of diatomaceous earth and filtered, and the filtrate was concentrated under reduced pressure to approximately 400 mL. After cooling, 38.4 g (59%) of **9b**, mp 83.5–84.5 °C, was obtained. Anal. ($C_6H_8ClNO_2$) C, H, N.

Fluorometric Procedure for Determining Hydrolysis Half-Life Times of Methyldopa Esters. Samples of the esters (2.5×10^{-5} mol) and 2-mercaptoethanol (0.050 mL) were diluted to a final volume of 50.0 mL (5×10^{-4} M in ester) with a pH 7.40, 0.050 ionic strength phosphate buffer solution under N_2 at 37 °C. Solutions of esters capable of forming aldehydes upon hydrolysis also contained aldehyde trapping reagents such as dimedone or L-cysteine present at concentrations ranging from 2 to 5×10^{-3} M. Ester solutions were maintained at 37 °C under N_2. At specified times, aliquots were removed, rapidly frozen, and stored at −15 °C until analysis for liberated methyldopa by the fluorometric method of Roth.[7] The *o*-phthaldehyde solution was prepared by mixing an 0.050 M sodium tetraborate solution (pH adjusted to 9.50) (20 mL), absolute EtOH (1 mL) containing *o*-phthaldehyde (20 mg), and 2-mercaptoethanol (0.010 mL) and filtering through sintered glass.

In a typical run, a 5×10^{-4} M solution of methyldopa (0.050 mL) and five 0.050-mL portions of thawed hydrolysis aliquots were added to 1-cm path length fluorescence cuvettes containing the phthaldehyde solution (2.0 mL). After 20 min, fluorescence intensities of the solutions were measured at excitation and emission wavelengths of 340 and 455 nm. Fluorescence intensity of a reference solution, 4×10^6 M quinine in 0.1 N H_2SO_4, was also measured immediately before and after the above series of determinations.

All fluorescence data were adjusted to a standard fluorescence intensity of the reference fluorescence solution. Ratios were then calculated of the intensity of fluorescence produced upon addition of the hydrolysis solution to the intensity of fluorescence produced upon addition of the methyldopa solution. A plot of this ratio, termed f^{20}, vs. the hydrolysis time, Δt_h, was then constructed. The 50% change in fluorescence ratio was calculated by means of the equation $f^{20}{}_{1/2} = (f^{20}{}_0 - f^{20}{}_\infty)/2$ where $f^{20}{}_0$ and $f^{20}{}_\infty$ are the initial and final fluorescence ratios. From the plot of f^{20} vs. Δt_h, the time required to reach $f^{20}{}_{1/2}$, termed $t_{1/2}$, was found.

Antihypertensive (SH Rat) Assay. The compounds were evaluated for their effect on the mean arterial pressure in conscious spontaneously hypertensive (SH) rats by a direct recording technique of Watson and Ludden.[10] The animals were purchased from Charles River (Lakeview) Laboratories, Wilmington, Md. Only male rats of 290–350-g body weight and 30–40 weeks of age were used. The compounds were administered orally after three control pressure readings.

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References and Notes

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