6-Alkyl Derivatives of 3-(3,4-Dihydroxyphenyl)alanine (Dopa). Part I. Synthesis *via* Oxazolinones

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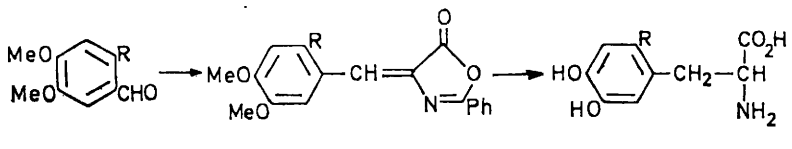
3-(3,4-Dihydroxyphenyl)alanines with a methyl, ethyl, or isopropyl group in the 6-position were obtained *via* the corresponding oxazolinones by an Erlenmeyer–Plöchl procedure. In the synthesis of 6-t-butyldopa (27) the intermediate α-benzamido-4,5-dimethoxy-2-t-butylcinnamic acid (21) was obtained in reasonable yield by treatment of the Grignard reagent from 5-t-butyl-4-bromoveratrole (11) with 4-ethoxymethylene-2-phenyl-Δ^2-oxazolin-5-one (18). The protecting groups (*N*-benzoyl and *O*-methyl) could be removed from the hydrogenated α-benzamidocinnamic acid without affecting the t-butyl group.

INHIBITORS of 3-(3,4-dihydroxyphenyl)alanine (dopa) decarboxylase have been the subject of extensive studies. Recent results with L-dopa in the treatment of Parkinson's disease have stimulated the investigation of compounds with inhibitory activity, especially in peripheral tissues.[1]

Alkyl substitution in the amino-acid side-chain of dopa gives potent inhibitors (*e.g.*, α-methyldopa). In order to establish to what extent increase in the size of the alkyl substituent in 6-alkyl derivatives affects their inhibitory activity, 6-methyl-, 6-ethyl-, 6-isopropyl-, and 6-t-butyl-dopa have now been synthesized.

The first three amino-acids (7)—(9) were prepared by an Erlenmeyer–Plöchl synthesis from the corresponding oxazolinones (4)—(6) as has been described for the methyl derivative (7) by Cromartie and his co-workers.[2] The alkyl-substituted veratraldehydes (1)—(3) were



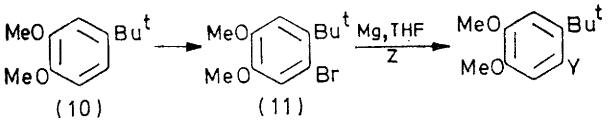
(1) - (3) (4) - (6) (7) - (9)

R = Me, Et, Pr^i

[1] 'Drugs for Parkinson's disease,' *Pharm. J.*, 1970, **204**, 513.
[2] R. I. T. Cromartie and J. Harley-Mason, *J. Chem. Soc.*, 1953, 3525.

obtained from the corresponding 4-alkylveratroles by Vilsmeyer formylations. The n.m.r. spectra of compounds (1)—(3) showed two singlets as expected [3] for two *para*-related aromatic protons. The structure of the intermediate oxazolinones (4)—(6) and their related α-benzamidocinnamates will be discussed in a subsequent paper [4] on the basis of their n.m.r. spectra.

An attempt was made to synthesize 6-t-butyldopa similarly, but Vilsmeyer formylation of 4-t-butylveratrole (10) did not afford the desired aldehyde. When the temperature was raised the methoxy-groups were attacked by phosphoryl chloride. Bromination of the t-butylveratrole (10) gave the 5-bromo-derivative (11) in good yield. In tetrahydrofuran the bromide could be almost entirely converted into the Grignard compound, as shown by carboxylation with carbon dioxide. The aldehyde (13) and methyl derivative (14) were prepared from the Grignard compound from (11).

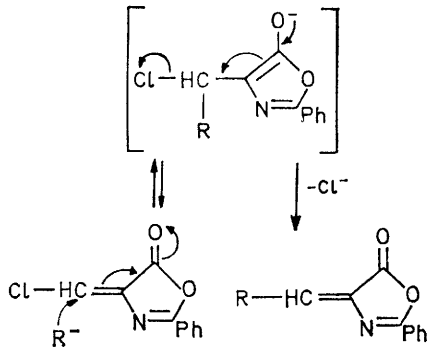


Z = CO_2 → Y = CO_2H (12)
Z = *N*-methylformanilide → Y = CHO (13)
Z = Me_2SO_4 → Y = Me (14)

Physical data for the methyl derivative (14) were in agreement with those given by Pospíšil *et al.*,[5] who obtained the same dialkylveratrole by t-butylation of 4-methylveratrole.

The absence of coupling between the aryl protons (see Table 1) of the substituted t-butylveratroles (11)—(14) indicates [3] the *para*-relationship, which was confirmed by n.m.r. comparison of the methyl-t-butylveratrole (14) with the two isomers with *meta*-related protons (see Table 1).

The yields of oxazolinone from condensation of 6-t-butylveratraldehyde (13) with hippuric acid were disappointing (*ca.* 10%). A more efficient synthesis is that of Behringer [6] who took advantage of reactivity of the methylene carbon atom in the chloromethyleneoxazolinone (15) toward nucleophiles, such as organometallic compounds of moderate reactivity (*e.g.*, magnesium compounds of indole and pyrrole and aryl-



(15)

cadmium compounds). In the case of aryl- and alkylmagnesium bromides Behringer observed competitive attack on the carbon atom of the carbonyl group.

Various conditions were tried to cause reaction of the Grignard compound from 4-bromo-5-t-butylveratrole (11) with the vinyl chloride (15) and with the vinyl ether (18), which is easier to prepare and produces markedly less tarry by-products. In addition to the desired oxazolinone (19), a colourless solid was isolated, which was identified as ethyl α-benzamido-4,5-dimethoxy-2-t-butylcinnamate (20). On replacing ethanol by methanol in the work-up the ethyl ester was again

TABLE 1

N.m.r. data for some substituted t-butylveratroles and t-butylcatechols (δ in p.p.m.) [a]

	Veratroles	Bu^t	Me	OMe/OH	ArH [b]
(11)	4-Br-5-Bu^t	1·47		3·81; 3·83	6·93; 7·02
(12)	4-Bu^t-5-CO_2H [c]	1·48		3·83; 3·85	6·92; 7·09
(13)	4-Bu^t-5-CHO [d]	1·49		3·82; 3·85	6·82; 7·38
(14)	5-Me-4-Bu^t [e]	1·35	2·40	3·73 (6H)	6·48; 6·77
	3-Me-5-Bu^t [e]	1·28	2·27	3·78; 3·85	6·80 (2H)
	5-Me-3-Bu^t [e]	1·32	2·27	3·79; 3·81	6·62; 6·68 ($J_{4,6}$ 1·5 Hz)
	Catechols				
(29)	5-Me-4-Bu^t	1·29	2·38	5·29 (2H)	6·63; 6·90
(30)	5-Me-3-Bu^t [f]	1·38	2·23	5·15 (2H)	6·54; 6·69 ($J_{4,6}$ 1·5—2 Hz)
	3-Me-5-Bu^t [f]	1·21	2·23	5·19; 5·46	6·73 (2H)
	6-Me-3-Bu^t [f]	1·38	2·18	4·78; 5·65	6·61; 6·78 ($J_{4,5}$ 8 Hz)

[a] Solvent $CDCl_3$; standard tetramethylsilane; temperature *ca.* 38°. [b] The aryl protons appeared as singlets, except where the coupling constant is given. [c] δ 12·10 (CO_2H). [d] δ 10·51 (CHO). [e] Prepared by methylation of the corresponding catechols; (3-Me-5-Bu^t) n_D^{20} 1·5052; (5-Me-3-Bu^t) n_D^{20} 1·5079 (Found for each compound: C, 74·9; H, 9·5. $C_{13}H_{20}O_2$ requires C, 75·0; H, 9·7%). [f] We thank M. Durkin, Coalite and Chemical Products Ltd., Chesterfield, Derbyshire, for providing samples of these catechols.

[3] H. Suhr, 'Anwendungen der kernmagnetischen Resonanz in der Organischen Chemie,' Springer-Verlag, Berlin, 1965, p. 164.

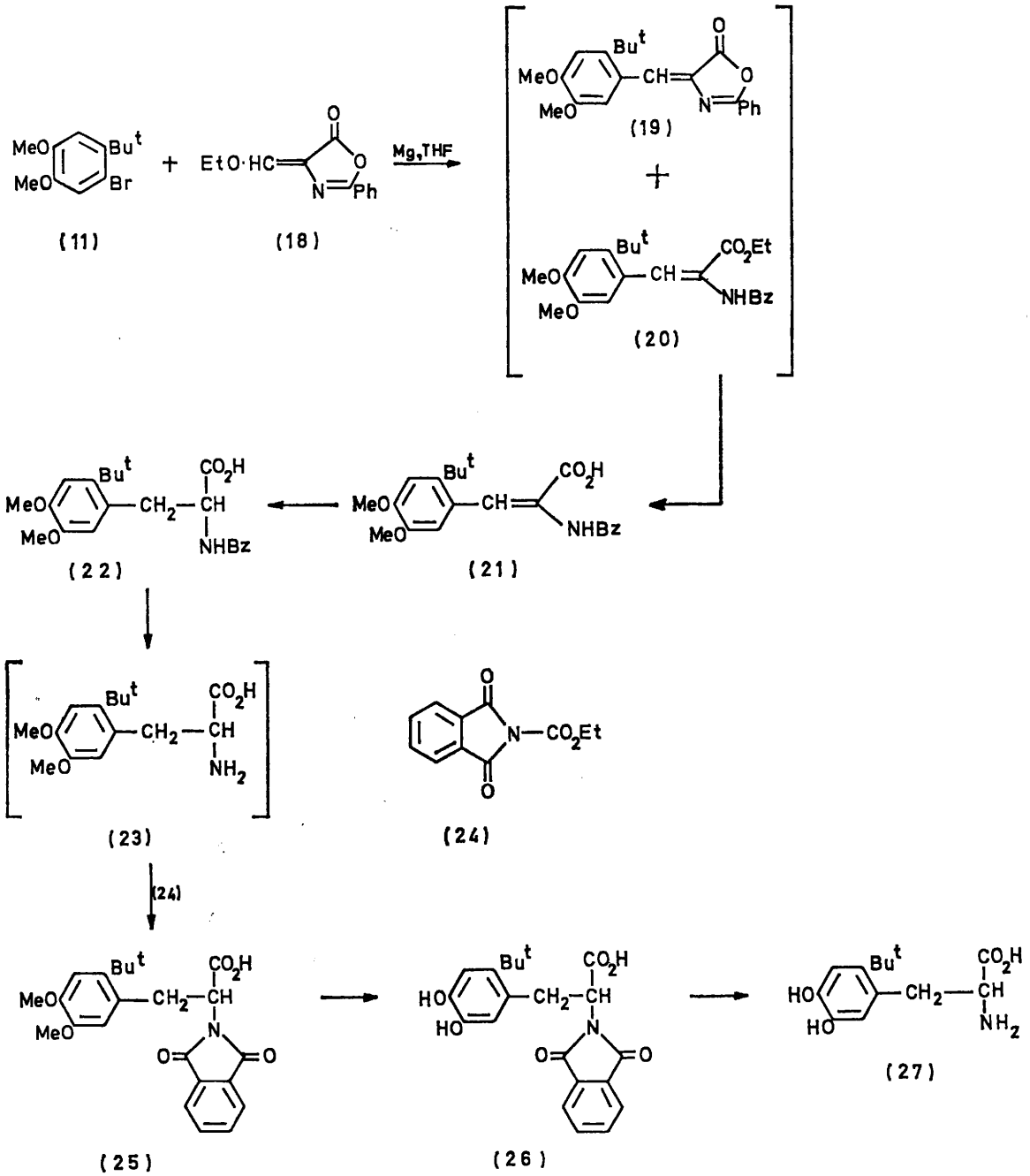
[4] Preliminary report, A. P. Morgenstern, C. Schuijt, and W. Th. Nauta, *Chem. Comm.*, 1969, 321.

[5] J. Pospíšil and L. Taimr, *Coll. Czech. Chem. Comm.*, 1965, **30**, 1092.

[6] H. Behringer and H. Taul, *Chem. Ber.*, 1957, **90**, 1398.

produced. It was therefore concluded that the oxazolinone ring is opened and the ester formed by attack (probably intermolecular) of the leaving ethoxide ion on the carbonyl carbon atom of the oxazolinone.

derivatives by addition of acetylenic Grignard reagents to the ethoxymethyleneoxazolinone (18). The esters were obtained in satisfactory yields but no formation of any corresponding oxazolinone was reported.



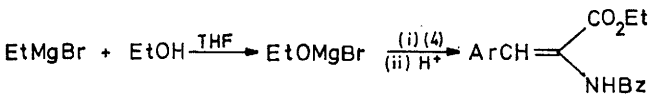
When a solution of the methylbenzylideneoxazolinone (4) in ether was treated with ethoxymagnesium bromide (16) in tetrahydrofuran, the corresponding ethyl α-benzamidocinnamate (17) was obtained, a result which supports the proposed intermolecular route.

Hiraoka and his co-workers [7] have reported the formation of ethyl esters of α-benzamidoacrylic acid

The t-butyl substituted benzylideneoxazolinone (19), also produced by treatment of the bromoveratrole (11) with the ethoxymethyleneoxazolinone (18), was identical with the material obtained in low yield from the Erlenmeyer–Plochl synthesis. Alkaline hydrolysis and esteri-

[7] T. Hiraoka and Y. Kishida, *Chem. and Pharm. Bull.* (*Japan*), 1968, **16**, 1576.

fication of this latter oxazolinone gave an ethyl ester which was identical with the ester (20) from the addition. We concluded that the t-butyl substituted oxazolinone



(16) (17)

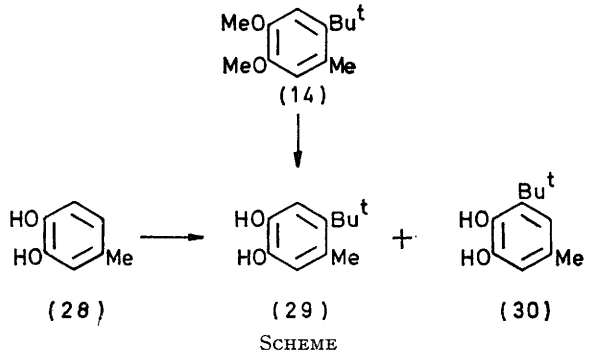
(19) and the ester (20) possessed the same geometric configuration.

Since it was possible to convert both (19) and (20) into the required α-benzamidocinnamic acid (21) by treatment with sodium hydroxide and acidification, it was not necessary to separate these two compounds.

By treating the hydrogenated α-benzamidocinnamic acid (22) with hydrohalic acids, both the protecting groups and the t-butyl group were removed. Even under mild conditions (2N-hydrochloric acid under reflux), when the benzoyl group was removed and the ether bonds remained intact, the t-butyl group was cleaved.

This inconvenient side reaction led us to study the removal of the *N*-benzoyl group in alkaline medium [8,9] and demethylation of the methoxy-groups by boron tribromide under mild conditions.[10] In order to establish whether boron tribromide caused any trans-alkylations [11] in the t-butyl-substituted veratrole system, 5-methyl-4-t-butylveratrole (14) was treated with this reagent under the conditions described.[10]

The expected catechol (29) should be identical with one of the products of the t-butylation of 4-methylcatechol (28).[5] The n.m.r. spectrum of the methyl-



(14)

(28) (29) (30)

SCHEME

t-butylcatechol (29) unambiguously confirmed the structure shown in the Scheme. Table 1 lists the n.m.r. spectral data for this compound and a number of isomeric methyl-t-butylcatechols.

For the conversion of the 3-aryl-*N*-benzoylalanine (22) into 6-t-butyldopa (27), debenzoylation with barium hydroxide had to be carried out before demethylation because of the affinity of the *ortho*-dihydroxy-groups for oxygen in alkaline medium. Isolation of the dimethoxy-amino-acid (23) after removal of the barium was facilitated by preparing the *N*-phthaloyl derivative (25) with ethyl 1,3-dioxoisoindoline-2-carboxylate (24).[12] The *N*-phthaloyl derivative (25) was demethylated with boron tribromide in dichloromethane, as already described. The phthaloyl group was removed with hydrazine; a reaction in which the *ortho*-hydroxy-groups were left unchanged. The overall yield of 6-t-butyldopa (27) from 4-t-butylcatechol was 4·5%.

EXPERIMENTAL

M.p.s were obtained with a Reichert hot-stage microscope. I.r. spectra were measured with a Perkin-Elmer 237 spectrophotometer. N.m.r. spectra were recorded with a Varian A-60A machine at *ca.* 38° [tetramethylsilane or sodium 3-(trimethylsilyl)propanesulphonate as internal standard].

Formylation of 4-Alkylveratroles.—Vilsmeyer formylations were performed as described by Bruce [13] for the methyl derivative (1) to give 6-methylveratraldehyde (1), m.p. 72—74° (lit.,[13] 72—73°) (62%), δ ($CDCl_3$) 2·58 (Me), 3·86 and 3·89 (each 3H, s, OMe), 6·65, and 7·28 (each 1H, s, ArH), and 10·12 (1H, s, CHO); and 6-ethylveratraldehyde (2), m.p. 24—26° (lit.,[14] 26°) (45%), δ ($CDCl_3$) 1·28 and 3·01 (Et), 3·89 and 3·93 (each 3H, s, OMe), 6·70 and 7·34 (each 1H, s, ArH), and 10·21 (1H, s, CHO) p.p.m. [semicarbazone, m.p. 197—199° (lit.,[14] 198°)].

6-Isopropylveratraldehyde (3).—4-Isopropylcatechol was methylated as described by Baker [15] under nitrogen in anhydrous acetone–benzene–potassium carbonate with vigorous stirring. In order to remove the small amount of alkylguaiacol, left in the crude distilled alkylveratrole, the crude oil was dissolved in benzene or toluene and vigorously stirred with 10—20% aqueous potassium hydroxide at room temperature for 2 h. After separation of the organic layer, washing, and distillation, a product was obtained that no longer showed an OH band in the i.r. spectrum at *ca.* 3500 cm^{-1}. *4-Isopropylveratrole,* b.p. 117—120° at 11 mmHg, n_D^{20} 1·5170 (80%), was formylated as described above. The crude *aldehyde,* obtained by extraction and subsequent distillation, was purified *via* its hydrogen sulphite addition compound, b.p. 121—126° at *ca.* 10^{-2} mmHg, n_D^{20} 1·5610 (*ca.* 20%), δ ($CDCl_3$) 1·27 and *ca.* 3·9 (Pr^i), 3·83 and 3·88 (each 3H, s, OMe), 6·80 and 7·24 (each 1H, s, ArH), and 10·18 p.p.m. (1H, CHO); *semicarbazone,* m.p. 178—181° (Found: C, 58·7; H, 7·3; N, 16·0. $C_{13}H_{19}N_3O_3$ requires C, 58·9; H, 7·2; N, 15·8%).

4-(2-Alkyl-4,5-dimethoxybenzylidene)-2-phenyl-Δ²-oxazolin-5-ones.[16]—These were synthesized by the method reported [17] for the unsubstituted dimethoxybenzylideneoxazolinone (see Table 2).

2-Alkyl-α-benzamido-4,5-dimethoxycinnamic Acids.—These were prepared by the procedure given by Cromartie [2] for the methyl derivative (see Table 3).

[8] L. A. Cohen and W. M. Jones, *J. Amer. Chem. Soc.*, 1962, **84**, 1629.
[9] H. Behringer and P. Duesberg, *Chem. Ber.*, 1963, **96**, 377.
[10] J. F. W. McOmie, M. L. Watts, and D. E. West, *Chem. and Ind.*, 1963, 1658; *Tetrahedron*, 1968, **24**, 2289.
[11] J. Pospíšil and M. Prusíková, *Coll. Czech. Chem. Comm.*, 1967, **32**, 2371; *Chem. and Ind.*, 1968, 1694.
[12] G. H. L. Nefkens, G. I. Tesser, and R. J. F. Nivard, *Rec. Trav. chim.*, 1960, **79**, 688.
[13] J. M. Bruce and F. K. Sutcliffe, *J. Chem. Soc.*, 1956, 3824.
[14] J. Ewing, G. K. Hughes, E. Ritchie, and W. C. Taylor, *Austral. J. Chem.*, 1953, **6**, 78.
[15] W. Baker and D. Miles, *J. Chem. Soc.*, 1955, 2089.
[16] N.m.r. spectra will be published in a subsequent paper.
[17] J. S. Buck and W. S. Ide, *Org. Synth.*, 1943, Coll. Vol. II, 55.

3-(2-*Alkyl*-4,5-*dimethoxyphenyl*)-N-*benzoylalanines*.— The cinnamic acid (0·015 mol) was shaken with Raney nickel in 0·25N-sodium hydroxide (250 ml) for 2 h under hydrogen (30 atm). The catalyst was filtered off. Acidification of the filtrate with hydrochloric acid afforded the dihydrocinnamic acid. In the case of the isopropyl and t-butyl derivatives complete hydrogenation could not be effected. dryness. The residual solid was dissolved in the minimum quantity of water, and the pH was adjusted to 5—6 with aqueous hydrogen carbonate. After filtration, the solution was cooled in a refrigerator for crystallization. The amino-acid sometimes required a few days to separate, and was recrystallized from water containing a trace of sulphur dioxide (see Table 5).

TABLE 2

Physical and analytical data for some 4-(2-alkyl-4,5-dimethyloxybenzylidene)-2-phenyl-Δ^2-oxazolinones

					Found (%)			Required (%)		
	2-Alkyl	M.p. (°C)	Yield (%)	Formula	C	H	N	C	H	N
(4)	Me	168—170 [a]	72	$C_{19}H_{17}NO_4$	70·4	5·3	4·3	70·6	5·3	4·3
(5)	Et	155—157 [b]	57	$C_{20}H_{19}NO_4$	71·3	5·7	4·4	71·2	5·7	4·2
(6)	Pr^i	162—164	53	$C_{21}H_{21}NO_4$	71·4	6·1	3·9	71·8	6·0	4·0
(19)	Bu^t	160—161	10 [c]	$C_{22}H_{23}NO_4$	72·5	6·4	3·7	72·3	6·3	3·8

[a] Lit.,[2] 167—168·5°. [b] Lit.,[18] 155°. [c] For the synthesis of 6-t-butylveratraldehyde (13) see text.

TABLE 3

Physical and analytical data for some 2-alkyl-α-benzamido-4,5-dimethoxycinnamic acids

				Found (%)			Required (%)		
2-Alkyl [a]	M.p. (decomp.) (°C)	Yield (%)	Formula	C	H	N	C	H	N
Me	214—216 [b]	84	$C_{19}H_{19}NO_5$	66·6	5·5	4·0	66·9	5·6	4·1
Et	210—212 [c]	75	$C_{20}H_{21}NO_5$	67·4	6·1	4·0	67·6	6·0	3·9
Pr^i	198—200	75	$C_{21}H_{23}NO_5$	68·5	6·3	3·7	68·3	6·3	3·8

[a] Bu^t synthesis and physical data described later. [b] Lit.,[2] 212—214°. [c] Lit.,[18] 212°.

TABLE 4

Physical and analytical data for some 3-(2-alkyl-4,5-dimethoxyphenyl)-*N*-benzoylalanines

					Found (%)			Required (%)		
	2-Alkyl	M.p. (decomp.) (°C)	Yield (%)	Formula	C	H	N	C	H	N
	Me	202 [a]	95	$C_{19}H_{21}NO_5$	66·2	6·3	4·3	66·5	6·2	4·1
	Et	186—188	90	$C_{20}H_{23}NO_5$	66·8	6·5	3·8	67·2	6·5	3·9
	Pr^i	177—180	90	$C_{21}H_{25}NO_5$	67·7	6·8	3·7	67·9	6·8	3·8
(22)	Bu^t	185—188	80	$C_{22}H_{27}NO_5$	68·4	7·1	3·5	68·6	7·1	3·6

[a] Lit.,[2] 203°.

TABLE 5

Physical and analytical data for some 3-(2-alkyl-4,5-dihydroxyphenyl)alanines

					Found [a] (%)			Required (%)		
	2-Alkyl	M.p. (decomp.) (°C)	Yield (%)	Formula	C	H	N	C	H	N
(7)	Me	*ca.* 265 [b]	57	$C_{10}H_{13}NO_4$	56·6	6·3	6·5	56·9	6·2	6·6
(8)	Et	*ca.* 260	45	$C_{11}H_{15}NO_4$	58·8	6·8	6·1	58·7	6·7	6·2
(9)	Pr^i	*ca.* 250	56	$C_{12}H_{17}NO_4$	60·0	7·1	5·9	60·2	7·2	5·9

	δ/p.p.m.: 2-Alkyl [c]	β-CH_2 (m)	α-CH (m)	ArH (s)
(7)	Me 2·19	3·15	4·21	6·73; 6·77
(8)	Et 1·16; 2·55	3·18	4·23	6·76; 6·82
(9)	Pr^i 1·22; 2·75—3·75		4·30	6·88; 7·02

[a] After drying (P_2O_5) at 100° and *ca.* 10^{-1} mmHg for 4 h. [b] Lit.,[2] 269°. [c] In D_2O–DCl

By treating an alkaline solution of the cinnamic acid with nickel–aluminium alloy,[19] a fully hydrogenated product could be obtained (as shown by the u.v. spectra). Data are given in Table 4.

3-(2-*Alkyl*-4,5-*dihydroxyphenyl*)*alanines*.—The *N*-benzoyl-dimethoxyphenylalanine (5 g) was heated under reflux with freshly distilled aqueous 48% hydrobromic acid (65 ml) under nitrogen. After cooling and dilution with water, the solution was extracted with ether to remove the benzoic acid, and evaporated to dryness under reduced pressure as rapidly as possible at *ca.* 60°. Water was then added and the resulting solution was again evaporated to

4-*Bromo*-5-*t*-*butylveratrole* (11).—Methylation of 4-t-butylcatechol as described for the foregoing isopropyl derivative afforded 4-t-butylveratrole, b.p. 114—118° at 9 mmHg, m.p. 34—35·5° (lit.,[20] 36—37°) [from light petroleum (b.p. 28—40°)] (85%). To a solution of t-butylveratrole (20 g) in anhydrous carbon tetrachloride (35 ml), cooled to −20°, was added a solution of bromine (16·8 g) in carbon tetrachloride (25 ml) at such a rate that the temperature of the

[18] G. Barger and R. Silberschmidt, *J. Chem. Soc.*, 1928, 2919.
[19] G. A. Nikiforov and K. M. Dyumaev, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1964, 1068.
[20] R. H. Rosenwald, *J. Amer. Chem. Soc.*, 1952, **74**, 4602.

flask did not exceed −10°. After addition of an aqueous solution of sodium hydrogen sulphite the organic layer was separated, washed, and dried. Distillation at 157—159° and 12 mmHg gave the crude *bromide*, m.p. 65—66° (from methanol–water) (80%); g.l.c. and t.l.c. showed a single compound (Found: C, 52·9; H, 6·4; Br, 29·5. $C_{12}H_{17}BrO_2$ requires C, 52·8; H, 6·3; Br, 29·3%).

6-*t-Butylveratric acid* (12).—To magnesium (20 mmol) in anhydrous tetrahydrofuran were slowly added 4-bromo-5-t-butylveratrole (11) (15 mmol) and dibromoethane (5 mmol) in such a volume of anhydrous tetrahydrofuran that the total volume was 15—20 ml. The mixture was heated under reflux under nitrogen for several h. Carbon dioxide was then passed through at *ca.* 70° for 12 h, and the mixture thus obtained was poured onto dilute hydrochloric acid. An ether extract was extracted with 2N-sodium hydroxide and acidification of the resultant alkaline extract gave the crude *veratric acid* (*ca.* 50%), m.p. 98—100·5° (from light petroleum) (Found: C, 65·3; H, 7·7. $C_{13}H_{18}O_4$ requires C, 65·5; H, 7·6%). The remaining ether extract was washed, dried, and evaporated to give 4-t-butylveratrole (50%), identified by i.r. spectroscopy.

6-*t-Butylveratraldehyde* (13).—To the tetrahydrofuran solution of the foregoing Grignard reagent was slowly added *N*-methylformanilide (0·03 mol). The volume of the solvent was increased to 30 ml and the mixture was stirred under nitrogen at room temperature for 18 h. It was then poured into dilute sulphuric acid at 0°, and stirred at room temperature for a further 1 h. Extraction with benzene and distillation at 97—103° and 10^{-3} mmHg gave the crude *aldehyde* (*ca.* 50%) as a light yellow oil, n_D^{20} 1·5550, $\nu_{max.}$ ($CHCl_3$) 1665 (C=O) cm^{-1}. An attempt to convert the aldehyde into its hydrogen sulphite adduct failed; *semicarbazone*, m.p. 155—158° (Found: C, 59·7; H, 7·6; N, 14·7. $C_{14}H_{21}N_3O_3$ requires C, 60·2; H, 7·6; N, 15 ·0).

5-*Methyl*-4-*t-butylveratrole* (14).—A solution of dimethyl sulphate (0·028 mol) in tetrahydrofuran (20 ml) was added to the tetrahydrofuran solution of the Grignard reagent (see before) at 70° (bath temperature) during 1 h. The solution, in which a precipitate had formed, was heated with stirring for 19 h. Addition of 0·25N-hydrochloric acid (30 ml) gave a two-layer system, which was extracted several times with toluene. After being washed and dried the toluene extract was distilled to give an *oil* (2·4 g), b.p. 125—135° at 10 mmHg; g.l.c. (20% SE 30 column; 230°) showed that the oil consisted of 4-t-butylveratrole (35%) and 5-*methyl*-4-*t-butylveratrole* (65%). Collection of the latter fraction gave the methyl derivative in a reasonably pure state, m.p. 5—8° (lit.,[5] 6·5—9·5°), n_D^{20} 1·5212 (lit.,[5] 1·5196) (Found: C, 74·6; H, 9·5. Calc. for $C_{13}H_{20}O_2$: C, 75·0; H, 9·7%).

α-*Benzamido*-4,5-*dimethoxy*-2-*t-butylcinnamic acid* (21) *and Ethyl Ester*[16] (20).—4-Bromo-5-t-butylveratrole (11) (15·3 g, 0·056 mol) was converted into the Grignard compound by treatment with dibromoethane (5 g, 0·027 mol) and magnesium (3—4 g) in anhydrous tetrahydrofuran (85 ml). The bluish-green solution was transferred into a well-dried dropping funnel by increasing the nitrogen pressure in the original three-necked flask; the tetrahydrofuran solution was thus forced into the funnel *via* a glass tube that reached to the bottom of the flask, and the excess of magnesium was left behind. The Grignard solution was then added during 15 min to a vigorously stirred solution of 4-ethoxymethylene-2-phenyl-Δ²-oxazolin-5-one[6] (18) (130·0 g, 0·06 mol) in anhydrous ether (*ca.* 500 ml). The mixture was heated under reflux for 1 h. Air was rigorously excluded from the apparatus. The red, half-solid mass in the yellow ethereal solution was poured into water, and the mixture was acidified (litmus) with 4N-acetic acid. The toluene–chloroform extracts of the aqueous layer were combined with the ether fraction, and the whole was washed and dried. The solvents were removed leaving a brownish red oil [the i.r. spectrum ($CHCl_3$) showed several strong bands in the range 1600—1800 cm^{-1} (C=O and C=N)]. The oil was worked up in two manners: for identification, (*A*), and for preparative purposes, (*B*).

(*A*) A solution of the oil in hot ethanol–methanol was cooled to give crystals of the dimethoxy-t-butylbenzylideneoxazolinone (19) (*ca.* 13%). After the crystals had been filtered off, the alcoholic filtrate was evaporated and the residue was stirred with aqueous sodium hydroxide (3%; 75 ml) and ethanol–methanol (*ca.* 100 ml). After some time the *ethyl cinnamate* separated, m.p. 147—149° (from chloroform–light petroleum), $\nu_{max.}$ ($CHCl_3$) 3430 (NH), 1715 (C=O ester), and 1675 (C=O NHBz) cm^{-1} (Found: C, 70·2; H, 7·1; N, 3·5. $C_{24}H_{29}NO_5$ requires C, 70·0; H, 7·1; N, 3·4%). Heating of the cinnamic acid (21) with ethanol and sulphuric acid gave an identical compound (20).

(*B*) Treatment of the oil with aqueous sodium hydroxide (5%; 125 ml) and ethanol (125 ml) at 60—80° for 1 h, cooling, evaporation of the alcohol, washing with ether, filtration, and acidification gave the *benzamidocinnamic acid* (21) (45%), m.p. 188—192° (decomp.) (from ethanol–water), δ ([$^2H_6$]Me_2CO) 7·11, 7·23, and 8·25 (each 1H, s, ArH and =CH), 3·62 and 3·85 (each 3H, s, OMe), and 1·44 (9H, s, Bu^t) (Found: C, 68·9; H, 6·7; N, 3·7. $C_{22}H_{25}NO_5$ requires C, 68·9; H, 6·6; N, 3·7%).

Reaction of Ethoxymagnesium Bromide (16) *with the Methyloxazolinone* (4).—Ethoxymagnesium bromide was prepared by addition of ethyl bromide (0·01 mol) to magnesium (0·01 mol) in tetrahydrofuran followed by the addition of ethanol (0·01 mol). As described for the cinnamic acid (21), the resultant mixture was forced under nitrogen into an ethereal solution of 4-(4,5-dimethoxy-2-methylbenzylidene)-2-phenyl-Δ²-oxazolin-5-one (4) (0·01 mol). Work-up gave a mixture of the starting oxazolinone (4) and ethyl α-benzamido-4,5-dimethoxy-2-methylcinnamate (17). Crystallization of the oxazolinone–ester mixture yielded the ester[16] (17) (55%), m.p. 133—135° (Found: C, 68·3; H, 6·2; N, 3·7. Calc. for $C_{21}H_{23}NO_5$: C, 68·3; H, 6·3; N, 3·8%).

3-(4,5-*Dimethoxy*-2-*t-butylphenyl*)-N-*phthaloylalanine* (25).—The *N*-benzoyl derivative (22) (3 g) was heated under reflux with aqueous barium hydroxide[9] under nitrogen for 5·5 days. The barium was precipitated by passing carbon dioxide through the mixture and acidifying the solution with dilute sulphuric acid to pH 4. After removal of the insoluble salts, the acidic solution was neutralized with aqueous hydrogen carbonate and then evaporated to dryness under reduced pressure. The remaining crude dimethoxy-t-butylphenylalanine (23) was washed with ether and then suspended in water (30 ml) while the pH was adjusted to 6—7. After addition of sodium carbonate (0·7 g) and ethyl 1,3-dioxoisoindoline-2-carboxylate[12] (24) (1·5 g), the flask was shaken for 15 min. Acidification of the filtered solution, gave the *phthaloylamino-acid* (50%), m.p. 191—193° (from ethanol–water), $\nu_{max.}$ ($CHCl_3$) 1720 and 1780 (C=O) cm^{-1}, δ ($CDCl_3$) 1·47 (9H, s, Bu^t),

3·39 and 3·83 (each 3H, s, OMe), 3·55—4·25 (2H, m, β-CH_2), 5·33 (1H, m, α-CH), 6·43 and 6·93 (each 1H, s, ArH), 7·79 (4H, m, phthaloyl H), and 10·0 (1H, CO_2H) (Found: C, 67·1; H, 6·3; N, 3·2. $C_{23}H_{25}NO_6$ requires C, 67·2; H, 6·1; N, 3·4%).

Demethylations with Boron Tribromide.—5-Methyl-4-t-butylveratrole (14) was demethylated [10] with boron tribromide at −60°. The mixture was stirred at this temperature for 1·5 h, then warmed to room temperature, poured on ice, and extracted with chloroform. Removal of the solvent, followed by addition of hexane, gave the derived *catechol*, m.p. 81—83°. The large difference in the m.p. (lit.,[5] 115—116°) induced us to reproduce Pospíšil's alkylation experiment: [5] 4-methylcatechol (28) was treated with t-butyl alcohol in acetic acid to give a mixture of alkyl-substituted catechols. T.l.c. and the n.m.r. spectrum of the mixture showed the presence of 5-methyl-3-t-butylcatechol (30) and *5-methyl-4-t-butylcatechol* (29) in the ratio 2 : 3. The latter was identical with the low-melting catechol isolated in the demethylation experiment. One recrystallization of the catechol with m.p. 81—83° (from hexane) raised the m.p. to 115—116°, as reported by Pospíšil [5] (Found: C, 73·3; H, 8·8. $C_{11}H_{16}O_2$ requires C, 73·3; H, 9·0%).

Demethylation of the *N*-phthaloyl derivative (1 g) of dimethoxy-t-butylphenylalanine (25) with boron tribromide (3·75 g) was carried out in dichloromethane (25 ml). The mixture was poured into ice–water and the dichloromethane removed *in vacuo*. From the residual acidic aqueous layer 3-(4,5-*dihydroxy*-2-*t*-*butylphenyl*)-N-*phthaloylalanine* (26) separated as a pale green solid, m.p. *ca.* 23° (decomp.) [from chloroform–ethanol–light petroleum (b.p. 80—100°)] (75%), $\nu_{max.}$ (KBr) 3480 (ArOH), 1730, and 1780 (C=O) cm^{-1}, δ ([$^2H_6$]Me_2SO) 1·33 (9H, s, Bu^t), 3·55 (2H, m, β-CH_2), 4·93 (1H, m, α-CH), 6·32 and 6·75 (each 1H, s, ArH), and 7·87 (4H, m, phthaloyl H) (Found: C, 65·4; H, 5·5; N, 3·7. $C_{21}H_{21}NO_6$ requires C, 65·8; H, 5·5; N, 3·7%).

3-(4,5-*Dihydroxy*-2-*t*-*butylphenyl*)*alanine* (6-*t*-*Butyldopa*) (27).—After the above *N*-phthaloyldihydroxyphenylalanine (26) (0·7 g) had been heated under reflux with hydrazine hydrate (0·25 g) in ethanol (10 ml) under nitrogen for 1 h,[21] the ethanol was removed *in vacuo* and 2N-hydrochloric acid (9 ml) was added. The mixture was heated at 50° for 15 min and then cooled. The phthalazine was filtered off. The filtrate was neutralized with hydrogen carbonate to pH 6 and the aqueous solution concentrated to a small volume, whereupon at pH 5·5 the *amino-acid* crystallized. Recrystallization from water with a trace of sulphur dioxide or precipitation from a solution made by acidification of a suspension of the compound in water until all the solid had dissolved, followed by neutralization with hydrogen carbonate to pH 5·5, afforded pure 6-*t*-*butyldopa*, m.p. *ca.* 250° (decomp.) (50%), δ (D_2O–DCl) 1·38 (9H, s, Bu^t), 3·52 (2H, m. β-CH_2), 4·46 (1H, m, α-CH), and 6·89 and 7·09 (each 1H, s, ArH) [Found (sample dried at 100° and 1 mmHg over P_2O_5 for 24 h): C, 61·5; H, 7·6; N, 5·6. $C_{13}H_{19}NO_4$ requires C, 61·7; H, 7·6; N, 5·5%].

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