Synthesis and Reactivity of Vinyl Quinone Methides

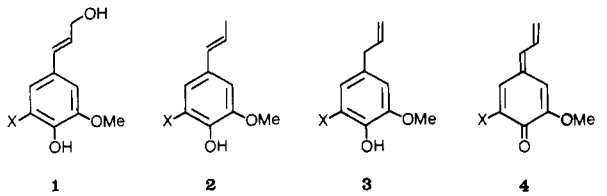
Antonio Zanarotti

CNR Centro di Studio per le Sostanze Organiche Naturali, Dipartimento di Chimica, Politecnico di Milano, 20133 Milano, Italy

Received June 26, 1984

Vinyl quinone methides **4a** and **4b** were obtained in high yields by Ag_2O oxidation of eugenol (**3a**) and of 2,6-dimethoxy-4-(2-propenyl)phenol (**3b**). Vinyl quinone methides (VQMs) reacted with alcohols, with phenols, and with acetic acid giving compounds **5** and **6**. As the former rearranged to the latter in the reaction medium, the addition of the reported substrates to VQMs turned out to be wholly regioselective toward the formation of the coniferyl and sinapyl derivatives **6**. In contrast, addition of carbon nucleophiles (acetylacetone and $EtNO_2$) to VQMs gave both compounds **7** and **8**. By reaction of the acetates **6a** and **6b** (R = CH_3CO) with $LiAlH_4$ it was possible to perform a novel synthesis of coniferyl and sinapyl alcohols (**1a** and **1b**). Treatment of the same acetates with an aqueous solution of $NaHCO_3$ reproduced VQMs **4**, which by subsequent reduction with $NaBH_4$ gave propenylphenols **2** and allylphenols **3**. Formation of the latter compounds from coniferyl and sinapyl acetates via VQM is here proposed as a possible biosynthetic pathway.

Quinone methides derived from dimerization of phenoxy radicals are recognized as transient intermediates in the biosynthesis of many natural substances.[1] For instance, the one-electron oxidation of C_6C_3 phenol units **1–3** leads to dimers (lignans and neolignans)[1,2] and to polymers (lignin)[1] via quinone methide intermediates.



1 **2** **3** **4**

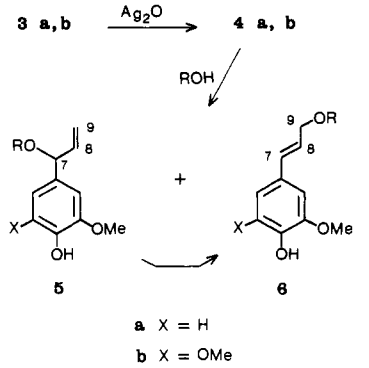
a X = H

b X = OMe

The biosynthetic and synthetic significance of such quinone methides is well recognized,[2,3] whereas little attention has been paid to the possible biosynthetic and synthetic role of quinone methides of the type **4**, which can derive from a two-electron oxidation of propenylphenols **2** and allylphenols **3** or from dehydration of alcohols **1**. Vinyl quinone methides (VQMs) **4** were reported to have been observed only by UV spectroscopy as transient intermediates in very diluted aqueous solution during the enzymatic oxidation of eugenol[4] (**3a**) or in the flash photolysis of coniferyl (**1a**) and sinapyl (**1b**) alcohols.[5]

In the present paper[6] VQMs **4** are reported to have been synthetized and characterized for the first time.[7] These reactive compounds may be phenylpropanoid building bloks (derived in nature from phenylalanine) which are biosynthetic precurs of lignin, lignans, neolignans, stilbenes, and flavonoids. The aim of the present research was to explore their reactivity toward selected nucleophiles in order to evaluate their utility as intermediates for synthesis of these natural product classes.

Scheme I



a X = H

b X = OMe

Table I. Reactions of 4a and 4b with Hydroxy Compounds[a]

entry	VQM, 3 mmol	ROH, mmol	R	product[b] (% yield)[d]	5:6 ratio[c] (total % yield)[d]
1	**4a**	250	Me	**6a**[e] (80)	3.1 (78)
2	**4a**	170	Et	**6a** (80)	3.2 (76)
3	**4a**	14	$PhCH_2$	**6a**[e] (76)	1.5 (70)
4	**4a**	14	$PhCH{=}CHCH_2$	**6a**[e] (71)	1.8 (72)
5	**4b**	250	Me	**6b** (89)	2.2 (86)
6	**4b**	170	Et	**6b** (90)	2.3 (88)
7	**4b**	14	$PhCH_2$	**6b** (81)	2.4 (75)
8	**4b**	14	$PhCH{=}CHCH_2$	**6b**[f] (79)	2.8 (80)
9	**4a**	12	Ph	**6a**[e] (45)	
10	**4a**	12	$2\text{-}OMeC_6H_4$	**6a**[e] (38)	
11	**4a**	12	$4\text{-}OMeC_6H_4$	**6a**[e] (54)	
12	**4b**	12	Ph	**6b** (75)	
13	**4b**	12	$2\text{-}OMeC_6H_4$	**6b**[e] (40)	
14	**4b**	12	$4\text{-}OMeC_6H_4$	**6b** (71)	
15	**4b**	12	$4\text{-}NO_2C_6H_4$	**6b** (20)	
16	**4a**	230	CH_3CO	**6a** (80)	
17	**4b**	230	CH_3CO	**6b** (80)	

[a] The reactions of **4a** have been performed in CCl_4 (80 mL), those of **4b** in benzene (40 mL). Catalysts: entries 1 and 5 PTSA (2.3×10^{-2} mmol), entries 2–4 and 6–8 PTSA (1.5×10^{-2} mmol), entries 9–15 Et_3N (0.4 mmol). [b] Reaction time 1–12 h. [c] Reaction time 10–120 s. [d] Yields based on isolated products and calculated on the starting phenols **3a** and **3b**. [e] Compound characterized as its acetyl derivative. [f] Compound characterized as its methyl derivative.

Results

Synthesis of VQMs 4a and 4b. Oxidation of eugenol (**3a**) in CCl_4 (1 g in 160 mL) at 65 °C with a large excess of Ag_2O gave VQM **4a** in a yield of over 90%.[8] VQM **4b**

(1) "Oxidative Coupling of Phenols"; Taylor, W. I., Battersby, A. R., Eds.; Marcel Dekker: New York, 1967.

(2) (a) Gottlieb, O. R. *Fortschr. Chem. Org. Naturst.* **1978**, *35*, 1. (b) Ward, R. S. *Chem. Soc. Rev.* **1982**, *11*, 75. (c) Zanarotti, A. *J. Chem. Res. Synop.* **1983**, 306.

(3) For reviews on quinone methids, see: (a) Wagner, H. U.; Gompper, R. In "The Chemistry of Quinonoid Compounds"; Patai, S., Ed.; J. Wiley and Son: London, New York, 1974; Chapter 18. (b) Gruenanger, P. In "Houben-Weyl Methoden der Organischen Chemie"; Mueller, E., Bayer, O., Eds.; G. Thieme Verlag: Stuttgard, 1979; Vol. VII/3b, p 395.

(4) Pew, J. C.; Connors, W. J.; Kunishi, A. In "Chimie et Biochimie de la Lignin, de la Cellulose et des Hemicellulose"; Acte du Symposim International de Grenoble, Juillet 1964; Impimeries Reunies: Grenoble, 1965; p 229.

(5) Leary, G. *J. Chem. Soc., Perkin Trans. 2* **1972**, 640. Hemmingson, J. A.; Leary, G. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1584.

(6) Part of this work has been reported in a preliminary communication: Zanarotti, A. *Tetrahedron Lett.* **1982**, *23*, 3815.

(7) Only one synthesis and characterization of a VQM has been reported so far: Dyall, L. K.; Winstein, S. *J. Am. Chem. Soc.* **1972**, *94*, 2196.

0022-3263/85/1950-0941$01.50/0

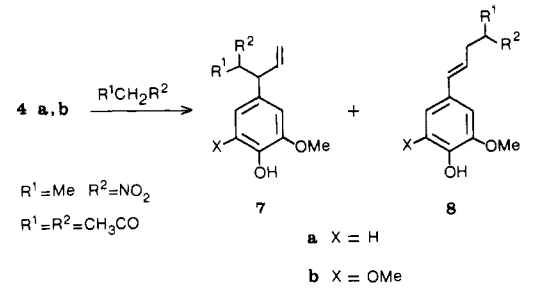
was obtained in the same way, at room temperature, in benzene or chloroform solution. At a concentration of 1 g in 80 mL compound **4b** is stable for hours at room temperature. The ^1H NMR analysis of the benzene or chloroform solution thus obtained showed that **4b** was formed in a quantitative yield.[9]

Reactivity of VQMs 4a and 4b. VQMs **4** reacted with primary alcohols, in the presence of traces of *p*-toluenesulfonic acid (PTSA), leading in 10–120 s to the regioisomers **5** and **6** (Scheme I, Table I entries 1–8); the couples of isomers were easily separated by flash chromatography. When the reactions were allowed to proceed for much longer times (6–12 h) only coniferyl and sinapyl ethers **6** were obtained as benzyl ethers **5** slowly rearranged to **6**. This was verified by isolating **5a** (R = Me) and **5b** (R = Et) from short-time reactions of **4a** and **4b** with MeOH and EtOH and treating the compounds with catalytic amounts of PTSA in the presence of MeOH or EtOH: **6a** (R = Me) and **6b** (R = Et) were obtained in quantitative yields.[10]

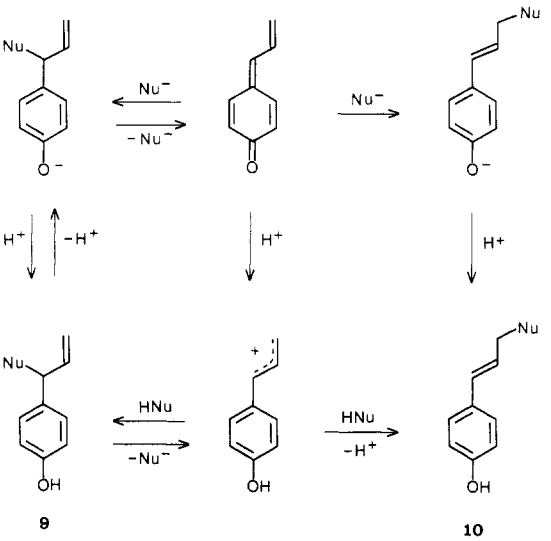
VQMs **4** reacted with phenols, in the presence of catalytic amounts of Et_3N,[11] leading to coniferyl and sinapyl ethers **6** within 1–4 h (Scheme I, Table I entries 9–15). All reactions showed the same trend: during the course of the reaction, the formation of ethers **6** (increasing amounts) and of a second unstable compound (decreasing) was observed by TLC. In one case (entry 11), the reaction was stopped before its completion by cooling and treating the mixture with Ac_2O and pyridine: the unstable transient compound was thus identified as the benzyl ether **5a** (R = 4-$OMeC_6H_4$) by isolation of its acetate.

A kinetically controlled formation of the two regioisomers occurred in the reaction of **4a** and **4b** with acetic acid as well; the unstable acetates **5a** (R = CH_3CO) and **5b** (R = CH_3CO), initially formed as the major isomers, rearranged to **6a** (R = CH_3CO) and **6b** (R = CH_3CO) in the reaction medium;[12] thus coniferyl and sinapyl acetates were obtained in 80% yield. The latter compounds gave respectively coniferyl (**1a**) and sinapyl (**1b**) alcohols in quantitative yields by treatment with $LiAlH_4$ in tetrahydrofuran. The fast procedure makes the described syntheses of coniferyl and sinapyl alcohols a convenient alternative to the previously reported method based on $LiAlH_4$ reduction of the esters of the corresponding acids.[13] Attempts to obtain alcohols **1a** and **1b** by hydrolysis of their acetates or by addition of water to VQMs proved unsuccessful; VQMs **4** appear to be more stable, in neutral or slightly basic aqueous solution, than coniferyl and sinapyl alcohols and their acetates.[14] Indeed, VQMs **4** were

Scheme II



Scheme III



stable for hours in neutral or slightly basic aqueous solution, and on the other hand, treatment of coniferyl and sinapyl acetates with an aqueous $NaHCO_3$ solution caused formation of VQMs **4a** and **4b**. This was confirmed by addition of $NaBH_4$ to the solution thus obtained: **6a** (R = CH_3CO) gave a mixture of eugenol (**3a**) and isoeugenol (**2a**) via **4a**, **6b** (R = CH_3CO) the corresponding mixture of **3b** and **2b** via **4b**. In fact, it was verified that the reduction of VQMs **4** with $NaBH_4$ led to mixtures of **2** and **3**. Product ratio was strongly dependent on the reaction medium; for example, the reductions performed in MeOH–water mixtures gave a **2**:**3** ratio changing from 0.5 to 2.0 for increasing amounts of MeOH in the solution; it is of interest to note that no traces of the *Z* isomers of **2a** and **2b** were detected by gas chromatographic analysis of the reaction mixtures, in agreement with the fact that for all the reactions in Table I no *Z* isomers of the compounds **6** were isolated.

Nitroethane and acetylacetone, used as substrates in order to test the reactivity of VQMs **4** toward carbon nucleophiles, gave the regioisomers **7** and **8** in a **8**:**7** ratio ≥2.7 (Scheme II). In these cases, in which the regioselectivity of the addition is exclusively under kinetic control as no rearrangements can occur, the attack at the less substituted end of the VQMs appears to be determined by the steric demands of the nucleophiles.

Discussion

The observed electrophilic reactivity of VQMs and the regioselectivity of the additions (i.e., kinetically controlled preferential attack at the benzylic position and selectivity toward 1,8-addition for thermodynamically controlled re-

(8) The synthesis of VQM **4a**, which bears the substitution pattern most frequently found in nature in phenylpropanoid units, has demanded a thorough investigation of the reaction conditions in order to avoid the competitive oxygen–*o*-phenol coupling. Dimerization was minimized by using (1) a nonpolar solvent, (2) a rather diluted solution, (3) high temperature, (4) and a large excess of Ag_2O. Compound **4a** could not be fully characterized by ^1H NMR as the yield of the reaction was not quantitative, moreover the compound is present as a mixture of the *E* and *Z* isomers.

(9) In ref 6 was reported the ^1H NMR spectrum of **4b** in $CDCl_3$. Due to signals overlap a coupling constant of 2.0 Hz has been uncorrectly assigned to the protons in the 5- and 7-position; it is evident from the quite clear spectrum of **4b** in C_6D_6 now obtained that this coupling constant must be assigned to the protons in the 3- and 5-position as described in the Experimental Section.

(10) When reacted with PTSA and alcohol also the methyl derivative of **5a** (R = Me) rearranged to the methyl derivative of **6a** (R = Me) whereas, in the absence of alcohol, polymeric materials were obtained.

(11) Addition of VQM **4b** on the aromatic ring of phenols occured in the presence of acids: Zanarotti, A. *Tetrahedron Lett.* **1982**, *23*, 3963.

(12) **5a** (R = CH_3CO) was initially formed in a 68% yield. The compound was isolated as its acetyl derivative.

(13) Allen, C. F. H.; Bayers, J. R. *J. Am. Chem. Soc.* **1949**, *71*, 2683. Freudenberg, K.; Huebner, H. H. *Chem. Ber.* **1952**, *85*, 1181.

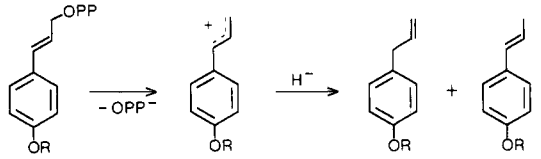
(14) Only polymeric materials were obtained by treating VQMs **4** with acidic or strongly basic aqueous solutions.

Table II. Significant ^1H NMR Data of Compounds 5 and 6[a]

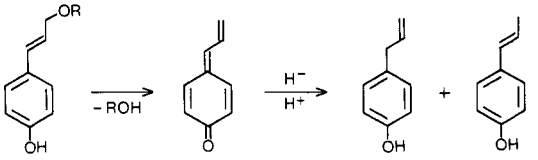
compd	H-7	H-8	H-9
5a,[b] R = Me	4.60 (d, 6.5)	5.87 (ddd, 6.5, 10.2, 16.2)	5.22 (m)
5a,[b] R = Et	4.71 (d, 6.8)	5.92 (ddd, 6.6, 10.2, 17.1)	5.18 (m)
5a,[b] R = $PhCH_2$	4.80 (d, 6.5)	5.90 (ddd, 6.5, 10.0, 17.2)	5.25 (m)
5a,[b] R = $PhCH{=}CHCH_2$	4.81 (d, 6.8)	5.90 (ddd, 6.8, 10.5, 17.0)	5.25 (m)
5b, R = Me	4.53 (d, 6.6)	5.90 (ddd, 6.6, 10.2, 16.2)	5.21 (m)
5b, R = Et	4.63 (d, 6.6)	5.90 (ddd, 6.6, 10.2, 17.2)	5.20 (m)
5b, R = $PhCH_2$	4.74 (d, 6.2)	6.00 (ddd, 6.2, 10.0, 17.2)	5.25 (m)
5b, R = $PhCH{=}CHCH_2$	4.79 (d, 6.5)	6.00 (ddd, 6.5, 10.0, 17.0)	5.25 (m)
5a,[b] R = 4-$OMeC_6H_4$	5.43 (d, 6.0)	6.03 (ddd, 6.0, 10.2, 16.2)	5.25 (m)
5a,[b] R = CH_3CO	6.26 (d, 5.7)	5.97 (ddd, 5.7, 10.0, 16.6)	5.22 (m)
6a,[b] R = Me	6.58 (d, 15.7)	6.20 (dt, 5.3, 15.7)	4.05 (d, 5.3)
6a, R = Et	6.50 (d, 15.8)	6.10 (dt, 6.0, 15.9)	4.08 (d, 6.0)
6a,[b] R = $PhCH_2$	6.60 (d, 16.0)	6.26 (dt, 6.0, 16.0)	4.19 (d, 6.0)
6a,[b] R = $PhCH{=}CHCH_2$	6.63 (d, 15.6)	6.20 (m)	4.20 (d, 5.7)
6b, R = Me	6.53 (d, 15.7)	6.14 (dt, 6.0, 15.7)	4.06 (d, 6.0)
6b, R = Et	6.50 (d, 16.0)	6.17 (dt, 6.0, 16.0)	4.10 (d, 6.0)
6b, R = $PhCH_2$	6.54 (d, 16.0)	6.17 (dt, 6.0, 16.0)	4.28 (d, 6.0)
6b,[c] R = $PhCH{=}CHCH_2$	6.51 (d, 16.0)	6.25 (m)	4.10 (d, 5.7)
6a,[b] R = Ph	6.71 (d, 16.5)	6.32 (dt, 5.7, 16.5)	4.65 (d, 5.7)
6a,[b] R = 2-$OMeC_6H_4$	6.70 (d, 16.5)	6.38 (dt, 5.7, 16.5)	4.73 (d, 5.7)
6a,[b] R = 4-$OMeC_6H_4$	6.66 (d, 16.0)	6.30 (dt, 5.2, 16.0)	4.60 (d, 5.2)
6b, R = Ph	6.60 (d, 16.5)	6.25 (dt, 5.7, 16.5)	4.63 (d, 5.7)
6b,[b] R = 2-$OMeC_6H_4$	6.66 (d, 16.5)	6.36 (dt, 4.8, 16.5)	4.72 (d, 4.8)
6b, R = 4-$OMeC_6H_4$	6.60 (d, 16.0)	6.20 (dt, 5.2, 16.0)	4.58 (d, 5.2)
6b, R = 4-$NO_2C_6H_4$	6.70 (d, 16.0)	6.26 (dt, 5.4, 16.0)	4.78 (d, 5.4)
6a, R = CH_3CO	6.58 (d, 16.5)	6.10 (dt, 6.5, 16.5)	4.69 (d, 6.5)
6b, R = CH_3CO	6.56 (d, 15.5)	6.17 (dt, 6.0, 15.5)	4.70 (d, 6.0)

[a] Spectra were determined in $CDCl_3$ solution at 90 MHz; chemical shifts are expressed in ppm (δ) relative to internal Me_4Si, coupling constants J in Hz. [b] Compound characterized as its acetyl derivative. [c] Compound characterized as its methyl derivative.

Scheme IV



Scheme V



actions) might be explained when considering (1) the high value of charge separation in the π-system of *simple* *p*-quinone methides,[15,16] (2) the partial positive charge at the side chain of **4** has a higher density at the benzylic position than at the terminal carbon atom (it seems reasonable to assume that the charge has a relative distribution comparable to that of phenylallyl cation[17]), and (3) aromatic *p*-hydroxy compounds bearing a leaving group at the benzylic position are liable to 1,6-elimination giving *p*-quinone methides.[3b,18] On these bases, a reasonable pathway for the formation of 1,6-adducts (**9**) and of 1,8-adducts (**10**) is outlined in Scheme III.

The described results raise the interesting question of whether VQMs might play a role in phenylpropanoid metabolism; in particular in the biosynthesis of propenylphenols (**2**) and allylphenols (**3**) from cinnamyl alcohols **1**.[19,20] It has been proved, in fact, that coniferyl alcohol (**1a**) is the *immediate* precursor of eugenol (**3a**).[21] Birch has suggested[22] the biosynthetic hypothesis reported in Scheme IV; however the present results on the formation of VQMs from the acetates of cinnamyl alcohols **1** and on the reduction of VQMs **4** to phenols **2** and **3** lead to the alternative proposal that quinone methides of the type **4** might be the intermediates in the biosynthesis of allylphenols and propenylphenols from cinnamyl alcohols (Scheme V).

Experimental Section

General Methods. Yields, selected ^1H NMR data, UV, and mass spectral data of compounds **5** and **6** are given in Tables I, II, and III. Eugenol (**3a**) (Fluka) was used as received; **3b** (EGA-Chemie) was purified by distillation in vacuo; Ag_2O (Riedel-de Haën) was washed with water and dried in vacuo. Unless otherwise stated the reactions were performed at room temperature. The yields, based on isolated products, were calculated on the starting phenols **3a** and **3b**. Elemental analyses for all new compounds (C, H, N) were within acceptable limits.

Synthesis of 2-Methoxy-4-(2-propenylidene)-2,5-cyclohexadien-1-one (4a). Ag_2O (6 g, 26 mmol) was added to a vigorously stirred solution of **3a** (1 g, 6.1 mmol) in CCl_4 (160 mL) at 65 °C. When the reaction was complete (9–11 min; TLC, silica gel, hexane–ethyl acetate 1:1; **3a**, R_f 0.53; **4a**, R_f 0.16) the suspension was filtered through Celite and the solution was immediately used for a reaction with a nucleophilic substrate.

Synthesis of 2,6-Dimethoxy-4-(2-propenylidene)-2,5-cyclohexadien-1-one (4b). Ag_2O (2.4 g, 10.4 mmol) was added to a stirred solution of **3b** (1g, 5.1 mmol) in benzene or chloroform (40 mL). When the reaction was complete (6–8 min; TLC, silica

(15) The reported[3a] Hückel molecular orbital description assigns to *p*-quinone methides an exceptionally high value of charge separation: effective charge −0.68 on the oxygen atom and +0.39 on the exocyclic carbon atom.

(16) Musil, L.; Koutek, B.; Pišová, M.; Souček, M. *Collect. Czech. Chem. Commun.* **1981**, *46*, 1148.

(17) Trost, B. M.; Hung, M. H. *J. Am. Chem. Soc.* **1983**, *105*, 7757.

(18) Quick, J.; Crelling, J. K. *J. Org. Chem.* **1978**, *43*, 155. de la Mare, P. B. D.; Newman, P. A. *J. Chem. Soc., Perkin Trans. 2* **1984**, 231.

(19) The biosynthesis of **2** and **3** has been the object of some hypothesis and discussion and still remains to be clarified. As a matter of fact compounds of the type **2** and **3** coexist in several plants and there are no suggestions that they might be formed from different precursors.[20c]

(20) (a) Harborne, J. B. In "Biosynthesis"; Geissman, T. A., Ed.; The Chemical Society: London, 1972; Vol. 1, p 125. (b) *Ibid.* Bu'Lock, J. D. Ed.; 1976; Vol. 4, p 85. (c) *Ibid.* 1977; Vol 5, p 45. (d) *Ibid.* 1980; Vol. 6, p 52.

(21) Klischies, M.; Stöckigt, J.; Zenk, M. H. *J. Chem. Soc., Chem. Commun.* **1975**, 879.

(22) Birch, A. J.; Slaytor, M. *Chem. Ind. (London)* **1956**, 1524.

Table III. UV and Mass Spectral Data of Compounds 5 and 6

compd	UV (EtOH) λ_{max} nm (ϵ)	mass spectrum m/z (rel int)	mp, °C[a]
5a,[b] R = Me	273 (2550), 279 (2310)	236 (M^+, 11), 193 (100), 166 (45), 162 (41)	oil
5a,[b] R = Et	274 (2750), 280 (2630)	250 (M^+, 14), 207 (100), 163 (22), 131 (60)	oil
5a,[b] R = $PhCH_2$	273 (3770), 279 (3600)	312 (M^+, 8), 270 (54), 179 (100), 164 (62)	oil
5a,[b] R = $PhCH{=}CHCH_2$	252 (19 500), 292 (1500)	338 (M^+, 7), 266 (77), 174 (50), 163 (100)	oil
5b, R = Me	241 (7320), 270 (1720)	224 (M^+, 100), 197 (39), 193 (33), 161 (41)	oil
5b, R = Et	241 (7980), 267 (2190)	238 (M^+, 100), 194 (41), 160 (52), 148 (38)	oil
5b, R= $PhCH_2$	242 (7530)	300 (M^+, 67), 194 (100), 161 (27), 108 (16)	oil
5b, R = $PhCH{=}CHCH_2$	247 (26 730), 292 (2610)	362 (M^+, 51), 208 (40), 194 (100), 134 (35)	oil
5a,[b] R = 4-$OMeC_6H_4$	280 (6100)	328 (M^+, 16), 286 (14), 205 (65), 163 (100)	oil
5a,[b] R = CH_3CO	274 (2770), 279 (2640)	264 (M^+, 21), 222 (86), 180 (100), 162 (86)	oil
6a,[b] R = Me	254 (10 400), 293 (3990)	236 (M^+, 16), 194 (100), 163 (31), 131 (63)	oil
6a, R = Et	268 (12 200)	207 (M − 1, 77), 178 (81), 163 (66), 151 (100)	oil
6a,[b] R = $PhCH_2$	240 (12 820), 293 (7220)	312 (M^+, 23), 270 (55), 179 (100), 164 (75)	oil
6a,[b] R = $PhCH{=}CHCH_2$	254 (28 000), 292 (5070)	338 (M^+, 5), 266 (100), 177 (52), 174 (67)	oil
6b, R = Me	278 (14 350)	224 (M^+, 100), 209 (18), 193 (54), 161 (50)	85
6b, R = Et	277 (16 750)	238 (M^+, 100), 209 (27), 192 (23), 160 (23)	68
6b, R = $PhCH_2$	278 (14 540)	300 (M^+, 71), 194 (100), 108 (38), 92 (92)	oil
6b,[c] R = $PhCH{=}CHCH_2$	254 (21 800)	340 (M^+, 1), 222 (19), 196 (83), 181 (44)	oil
6a,[b] R = Ph	255 (18 700), 294 (4900)	298 (M^+, 4), 205 (61), 163 (87), 131 (100)	77
6a,[b] R = 2-$OMeC_6H_4$	255 (19 240), 291 (5250)	328 (M^+, 33), 286 (86), 124 (95), 109 (100)	87
6a,[b] R = 4-$OMeC_6H_4$	254 (21 800), 292 (9150)	328 (M^+, 95), 286 (100), 205 (50), 163 (80)	107
6b, R = Ph	278 (18 100)	286 (M^+, 57), 192 (100), 160 (87), 132 (52)	63
6b,[b] R = 2-$OMeC_6H_4$	267 (19 300)	358 (M^+, 19), 316 (100), 235 (42), 193 (54)	93
6b, R = 4-$OMeC_6H_4$	280 (19 000)	316 (M^+, 5), 193 (81), 161 (100), 147 (36)	125
6b, R = 4-$NO_2C_6H_4$			
6a, R = CH_3CO	268 (8190 294 (4160)	222 (M^+, 100), 179 (43), 163 (21), 131 (71)	50
6b, R = CH_3CO	280 (13 600)	252 (M^+, 100), 209 (20), 193 (12), 161 (20)	62

[a] All solid compounds crystallized from cyclohexane. [b] Compound characterized as its acetyl derivative. [c] Compound characterized as its methyl derivative.

gel, ethyl acetate–hexane 2:1; **3b**, R_f 0.52; **4b**, R_f 0.19) the suspension was filtered through Celite and the solution was used for a reaction with a nucleofilic substrate. For ^1H NMR analysis the oxidation of **3b** was performed in $CDCl_3$ or in C_6D_6 solution at a concentration of 25 mg/mL: IR ($CHCl_3$) 1633 (s), 1587 (m), 1573 (s), 1535 (m), 1340 (s), 1235 (m), 1110 (s), 935 (w) cm^{-1}; UV ($CHCl_3$) λ_{max} 285 nm (ϵ 12 800), 363 (700); ^1H NMR (C_6D_6) δ 3.01 and 3.06 (s, 3 H each, CH_3O), 5.02 (br d, 1 H, J_{cis} = 10.0 Hz, cis *H*CH=CH), 5.12 (br d, 1 H, J_{trans} = 16.0 Hz, trans *H*CH=CH), 5.60 (d, 1 H, J = 2.0 Hz, 3-H or 5-H), 5.92 (d, 1 H, J = 11.6 Hz, C*H*CH=CH_2), 6.10 (d, 1 H, J = 2.0 Hz, 5-H or 3-H), 6.50 (ddd, 1 H, J = 10.0, 11.6, 16.0 Hz, C*H*=CH_2).

Reactions of 4a and 4b with Alcohols. General Procedure. The amounts of reactants and solvents are given in Table I. The synthesis of **5b** (R = Me) and **6b** (R = Me) is given as a general procedure. To a benzene solution (40 mL) of **4b** (3.0 mmol) were added 10 mL of MeOH and then dropwise with stirring 3.9 mL of a 5.8 10^{-3} M solution of PTSA in benzene–tetrahydrofuran 5:2; the yellow solution turned water clear when the reaction was complete (2 min); TLC analysis showed the presence of **5b** (R = Me) and **6b** (R = Me); the former rearranged to the latter within 10 h after a further addition of 3.9 mL of the PTSA solution. Alternatively, the solution obtained from short-time reaction was washed with brine and concentrated in vacuo to leave an oil which was subjected to flash chromatography giving **5b** (R = Me) and **6b** (R = Me).

Reactions of 4a and 4b with Phenols. General Procedure. The reactions were performed by addition of a solution of 3.0 mmol of VQM to a solution of phenol (12 mmol) in CH_2Cl_2 (10 mL) containing Et_3N (0.04 mL). The reactions showed the course described in the text. When the reactions were complete (1–4 h) the solvent was removed in vacuo and the residual oil was subjected to chromatography or it was treated with Ac_2O and pyridine before the separation. The unstable compound **6b** (R = 4-$NO_2C_6H_4$) has been characterized only by ^1H NMR.

Synthesis of Coniferyl and Sinapyl Acetates (6a (R = CH_3CO) and 6b (R = CH_3CO)). A solution of 6.1 mmol of VQM (**4a** in 160 mL of CCl_4, **4b** in 80 mL of benzene) was treated with a suspension of 4 g of CH_3CO_2Na in 25 mL of acetic acid; the mixture was stirred for 40 min, then solid CH_3CO_2Na was filtered off, and the solution was concentrated in vacuo to 20 mL. The solution thus obtained was allowed to stand for 4 h and then was evaporated; the residue was filtered through 15 g of silica gel by eluting with hexane–ethyl acetate 1:1; evaporation of the solvent left an oil which crystallized on standing. The course of the reaction of **4a** with acetic acid was monitored by treating samples, drawn from the reaction mixtures at different times, with Ac_2O and pyridine. TLC analysis of the samples thus obtained showed the formation of two compounds: initially major isomer **5a** (R = CH_3CO) rearranged to the second one **6a** (R = CH_3CO) within 20 h. The rearrangement occurred in less than 4 h if CH_3CO_2Na and the solvent were removed from the reaction mixture as reported above.

Synthesis of Coniferyl (1a) and Sinapyl (1b) Alcohols. A solution of 4.0 mmol of **6a** (R = CH_3CO) or **6b** (R = CH_3CO) in dry tetrahydrofuran (THF, 10 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (310 mg) in THF (5 mL) at −10 °C under a nitrogen atmosphere. The suspension was stirred for 30 min at −10 °C and then 2 mL of ethyl acetate was added dropwise followed by 3 mL of wet THF, 20 mL of brine, and 20 mL of CH_2Cl_2. The water phase was neutralized with $KHSO_4$ and then extracted with CH_2Cl_2 (4 × 20 mL). To the dried organic layer was added 30 mL of toluene and the solution was concentrated in vacuo to 15 mL. Both alcohols were obtained in a quantitative yield by letting the toluene solution take in hexane vapors in a closed container. The described workup was performed keeping the temperature below 10 °C.

Reduction of 4a and 4b with $NaBH_4$. A solution of 0.30 mmol of VQM (**4a** in 8 mL of CCl_4, **4b** in 4 mL of benzene) was added dropwise to a solution of an excess of $NaBH_4$ (200 mg) in MeOH (10 mL) or in mixtures of MeOH and water. The disappearance of the yellow color of the VQM was immediate. The solution thus obtained was neutralized with $KHSO_4$, then extracted with ethyl acetate; the organic layer was dried over Na_2SO_4, then evaporated. GC analysis of the residual oil (column Pyrex WCO, OV-1, temperature from 110 to 150 °C) showed the presence of **2a** and **3a** for the reduction of **4a**, and of **2b** and **3b** for the reduction of **4b**. The overall yield was about 80%; the **2**:**3** ratio was variable as described in the Results section.

Reaction of 4a and 4b with Nitroethane. General Procedure. A solution of 3.0 mmol of VQM (**4a** in 80 mL of CCl_4, **4b** in 40 mL of benzene) was added to a mixture of $EtNO_2$ (10 mL) and Et_3N (0.1 mL). The end of the reaction (2 h for **4a**, 8 h for **4b**) was monitored by the disappearance of VQM observed by TLC. The solution was concentrated to 20 mL then treated with an excess of Ac_2O and pyridine. The excess of these reagents

was removed under high vacuum. The residue obtained was subjected to chromatography. From both VQMs were obtained three compounds: the major isomer derived from 1,8-addition and a pair of diastereoisomers derived from 1,6-addition.

2-Methoxy-4-(1-ethenyl-2-nitropropyl)phenol (7a, R^1 = Me, R^2 = NO_2) Acetate. Selected data. Erythro or threo isomer: yield 9%; mp 88–90 °C; ^1H NMR ($CDCl_3$) δ 3.70 (dd, 1 H, *J* = 8.1, 10.2 Hz, C*H*CH=CH_2), 4.81 (dq, 1 H, *J* = 6.3, 10.2 Hz, $CHNO_2$), 5.15 (m, 2 H, CH_2=CH), 5.92 (ddd, 1 H, *J* = 8.1, 10.3, 18.0 Hz, C*H*=CH_2). Other diastereoisomer: yield 12%; mp 105–110 °C; ^1H NMR ($CDCl_3$) δ 3.83 (dd, 1 H, *J* = 9.0, 9.0 Hz, C*H*CH=CH_2), 4.85 (dq, 1 H, *J* = 6.3, 9.0 Hz, $CHNO_2$), 5.20 (m, 2 H, CH_2=CH), 5.90 (ddd, 9.0, 10.3, 18.0 Hz, C*H*=CH_2).

(*E*)-2-Methoxy-4-(4-nitro-1-pentenyl)phenol (8a, R^1 = Me, R^2 = NO_2) Acetate: yield 56%; oil; IR (neat) 1545, 1263, 1195 cm^{-1}; UV (EtOH) λ_{max} 254 nm (ε 15 940), 293 (5180); ^1H NMR ($CDCl_3$) δ 1.52 (d, 3 H, *J* = 6.7 Hz, CH_3CH), 2.25 (s, 3 H, CH_3CO), 2.72 (m, 2 H, CH_2), 3.80 (s, 3 H, CH_3O), 4.62 (ddq, 1 H, *J* = 6.7, 6.7, 6.7 Hz, C*H*CH_3), 5.95 (dt, 1 H, *J* = 7.2, 16.5 Hz, CH_2C*H*=CH), 6.43 (d, 1 H, *J* = 16.5 Hz, C*H*=$CHCH_2$), 6.90 (br s, 3 H, aromatic H); MS, *m/z* (relative intensity) 279 (M^+, 22), 237 (96), 190 (100).

2,6-Dimethoxy-4-(1-ethenyl-2-nitropropyl)phenol (7b, R^1 = Me, R^2 = NO_2) Acetate. Selected data. Erythro or threo isomer: yield 10%; mp 132 °C; ^1H NMR δ 3.62 (dd, 1 H, *J* = 8.2, 10.2 Hz, C*H*CH=CH_2), 4.80 (dq, 1 H, 6.2, 10.2 Hz, $CHNO_2$), 5.15 (m, 2 H, CH_2=CH), 5.93 (ddd, 1 H, *J* = 8.2, 10.3, 18.0 Hz, C*H*=CH_2). Other diastereoisomer: yield 8%; mp 150–152 °C; ^1H NMR ($CDCl_3$) δ 3.83 (dd, 1 H, *J* = 8.5, 8.5 Hz, C*H*CH=CH_2), 4.82 (dq, 1 H, *J* = 6.2, 8.5 Hz, $CHNO_2$), 5.21 (m, 2 H, CH_2=CH), 5.88 (ddd, 1 H, *J* = 8.5, 10.3, 18.0 Hz, C*H*=CH_2).

(*E*)-2,6-Dimethoxy-4-(4-nitro-1-pentenyl)phenol (8b, R^1 = Me, R^2 = NO_2) Acetate: yield 60%; oil; IR (neat) 1725, 1190, 1130 cm^{-1}; UV (EtOH) λ_{max} 263 nm (ε 10 170); ^1H NMR ($CDCl_3$) δ 1.52 (d, 3 H, *J* = 6.6 Hz, CH_3CH), 2.31 (s, 3 H, CH_3CO), 2.72 (m, 2 H, CH_2), 3.79 (s, 6 H, CH_3O), 4.62 (m, 1 H, $CHNO_2$), 6.03 (dt, 1 H, *J* = 6.9, 16.5 Hz, C*H*CH_2), 6.40 (d, 1 H, 16.5 Hz, C*H*=$CHCH_2$), 6.60 (s, 2 H, aromatic H); MS, *m/z* (relative intensity) 309 (M^+, 10), 267 (100), 220 (58).

Reactions of 4a and 4b with Acetylacetone. General Procedure. A solution of 3.0 mmol of VQM (**4a** in 80 mL of CCl_4, **4b** in 40 mL of benzene) was added to a mixture of 1 mL of acetylacetone (10 mmol) and 0.02 mL of Et_3N. The end of the reaction (80 min for **4a**, 120 min for **4b**) was monitorized by the disappearance of VQM (TLC). The solution was evaporated and the residual oil was subjected to reverse-phase column chromatography (silica gel, Merck LiChroprep RP-18, 40 g, MeCN–water 1:1 as the eluant).

3-Acetyl-4-ethenyl-4-(4-hydroxy-3-methoxyphenyl)butan-2-one (7a, R^1 = R^2 = CH_3CO): yield 22%; mp 61–62 °C (cyclohexane); IR (Nujol) 1725, 1695, 1515 cm^{-1}; UV (EtOH) λ_{max} 283 nm (ε 3670); ^1H NMR ($CDCl_3$) δ 1.91 and 2.24 (s, 3 H each, CH_3CO), 3.87 (s, 3 H, CH_3O), 4.10 (dd, 1 H, *J* = 7.6, 11.6, C*H*CH=CH_2), 4.21 (d, 1 H, *J* = 11.6 Hz, C*H*$COCH_3$), 5.05 (m, 2 H, CH_2=CH), 5.58 (s, 1 H, OH), 5.85 (ddd, 1 H, *J* = 7.6, 10.0, 17.2 Hz, C*H*=CH_2), 6.67–6.84 (m, 3 H, aromatic H); MS, *m/z* (relative intensity) 262 (M^+, 14), 219 (64), 131 (100).

(*E*)-3-Acetyl-6-(4-hydroxy-3-methoxyphenyl)-5-hexen-2-one (8a, R^1 = R^2 = CH_3CO): yield 41%; mp 73–75 °C (cyclohexane); IR (Nujol) 1715, 1700, 1235 cm^{-1}; UV (EtOH) λ_{max} 267 nm (ε 15 680), 290 (sh, 9000); ^1H NMR ($CDCl_3$) δ 2.18 (s, 6 H, CH_3CO), 2.70 (m, 2 H, CH_2), 3.75 (t, 1 H, *J* = 7.2, C*H*$COCH_3$), 3.86 (s, 3 H, CH_3O), 5.60 (s, 1 H, OH), 5.86 (dt, 1 H, *J* = 5.2, 16.0 Hz, CH=C*H*CH_2), 6.35 (br d, *J* = 16.0 Hz, C*H*=$CHCH_2$), 6.80 (s, 3 H, aromatic H); MS, *m/z* (relative intensity) 262 (M^+, 22), 219 (57), 137 (100).

3-Acetyl-4-ethenyl-4-(4-hydroxy-3,5-dimethoxyphenyl)-butan-2-one (7b, R^1 = R^2 = CH_3CO) Acetate: yield 22%; mp 106 °C (cyclohexane); IR (KBr) 1795, 1220, 1143 cm^{-1}; UV (EtOH) λ_{max} 267 nm (ε 2640); ^1H NMR ($CDCl_3$) δ 1.92, 2.23, and 2.30 (s, 3 H each, CH_3CO), 3.80 (s, 6 H, CH_3O), 4.15 (dd, 1 H, *J* = 6.0, 11.4 Hz, C*H*CH=CH_2), 4.23 (d, 1 H, *J* = 11.4 Hz, C*H*$COCH_3$), 5.10 (m, 2 H, CH_2=CH), 5.88 (dddd, 1 H, *J* = 1.8, 6.0, 9.6, 16.8 Hz, C*H*=CH_2), 6.43 (s, 2 H, aromatic H); MS, *m/z* (relative intensity) 335 (M + 1, 15), 249 (95), 231 (90), 161 (100).

(*E*)-3-Acetyl-6-(4-hydroxy-3-methoxyphenyl)-5-hexen-2-one (8b, R^1 = R^2 = CH_3CO): yield 45%; oil; IR ($CHCl_3$) 1725, 1480, 1120 cm^{-1}; UV (EtOH) λ_{max} 272 nm (ε 12 750); ^1H NMR δ 2.18 (s, 6 H, CH_3CO), 2.70 (m, 2 H, CH_2), 3.76 (t, 1 H, *J* = 7.2 Hz, C*H*$COCH_3$), 3.87 (s, 6 H, CH_3O), 5.50 (s, 1 H, OH), 5.90 (dt, 1 H, *J* = 5.2, 16.0 Hz, CH=C*H*CH_2), 6.33 (br d, 1 H, *J* = 16.0 Hz, C*H*=$CHCH_2$), 6.52 (s, 2 H, aromatic H); MS, *m/z* (relative intensity) 292 (M^+, 2), 182 (22), 85 (69), 83 (100).

Registry No. **1a**, 32811-40-8; **1b**, 20675-96-1; **2a**, 5932-68-3; **2b**, 20675-95-0; **3a**, 97-53-0; **3b**, 6627-88-9; **4a**, 10570-85-1; **4b**, 58623-87-3; **5a** (R = Me, acetate), 94930-69-5; **5a** (R = Et, acetate), 94930-70-8; **5a** (R = $PhCH_2$, acetate), 94930-71-9; **5a** (R = PhCH=$CHCH_2$, acetate), 94930-72-0; **5a** (R = 4-$OMeC_6H_4$, acetate), 94930-73-1; **5a** (R = CH_3CO, acetate), 53890-24-7; **5b** (R = Me), 66463-74-9; **5b** (R = Et), 84700-94-7; **5b** (R = $PhCH_2$), 84700-95-8; **5b** (R = PhCH=$CHCH_2$), 84700-96-9; **6a** (R = Me, acetate), 94930-74-2; **6a** (R = Et), 94930-75-3; **6a** (R = $PhCH_2$, acetate), 94930-76-4; **6a** (R = PhCH=$CHCH_2$, acetate), 94930-77-5; **6a** (R = Ph, acetate), 94930-78-6; **6a** (R = 2-$OMeC_6H_4$, acetate), 94930-79-7; **6a** (R = 4-$OMeC_6H_4$, acetate), 94930-80-0; **6a** (R = CH_3CO), 94930-81-1; **6b** (R = Me), 94930-82-2; **6b** (R = Et), 94930-83-3; **6b** (R = $PhCH_2$), 94930-84-4; **6b** (R = PhCH=$CHCH_2$, Me ether), 94930-85-5; **6b** (R = Ph), 94930-86-6; **6b** (R = 2-$OMeC_6H_4$, acetate), 94930-87-7; **6b** (R = 4-$OMeC_6H_4$), 94930-88-8; **6b** (R = 4-$NO_2C_6H_4$), 94930-89-9; **6b** (R = CH_3CO), 94930-90-2; (*R*,R**)-**7a** (R^1 = Me, R^2 = NO_2, acetate), 94930-91-3; (*R*,S**)-**7a** (R^1 = Me, R^2 = NO_2, acetate), 94930-98-0; **7a** (R^1 = R^2 = CH_3CO), 94930-95-7; (*R*,R**)-**7b** (R^1 = Me, R^2 = NO_2, acetate), 94930-93-5; (*R*,S**)-**7b** (R^1 = Me, R^2 = NO_2, acetate), 94930-99-1; **7b** (R^1 = R^2 = CH_3CO, acetate), 94930-97-9; **8a** (R^1 = Me, R^2 = NO_2, acetate), 94930-92-4; **8a** (R = R^2 = CH_3CO), 94930-96-8; **8b** (R^1 = Me, R^2 = NO_2, acetate), 94930-94-6; **8b** (R^1 = R^2 = CH_3CO, acetate), 94956-21-5; MeOH, 67-56-1; EtOH, 64-17-5; $PhCH_2OH$, 100-51-6; PhCH=$CHCH_2OH$, 104-54-1; PhOH, 108-95-2; 2-$OMeC_6H_4OH$, 90-05-1; 4-$OMeC_6H_4OH$, 150-76-5; 4-$NO_2C_6H_4OH$, 100-02-7; CH_3CO_2H, 64-19-7; $EtNO_2$, 79-24-3; $CH_2(COCH_3)_2$, 123-54-6.

Chemoselective N-Ethylation of Boc Amino Acids without Racemization

Donald W. Hansen, Jr.* and Daniel Pilipauskas

Department of Medicinal Chemistry, Searle Research and Development, Division of G. D. Searle and Co., Skokie, Illinois 60077

Received June 18, 1984

The Boc derivatives of amino acids such as phenylalanine, methionine, and tyrosine benzyl ethers have been selectively ethylated to give, respectively, the enantiomerically pure Boc-*N*-ethyl amino acids **12**, **20**, and **23**. The benzyl, trimethylsilyl, and *tert*-butyldimethylsilyl groups were employed as transient protecting groups for the phenolic hydroxyl in the synthesis of Boc-Et-Tyr (**25**).

N-Substituted α-amino acids have not only been found to possess biological activity[1] but the substitution of N-alkyl α-amino acids into physiologically active peptides has led to materials with varied and enhanced biological ac-

0022-3263/85/1950-0945$01.50/0