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SYNTHETIC STUDIES ON THE LYTHRACEAE ALKALOIDS—IX[1]

VANADIUM (V) OXIDATION OF SOME SECO-ALKALOIDS[2]

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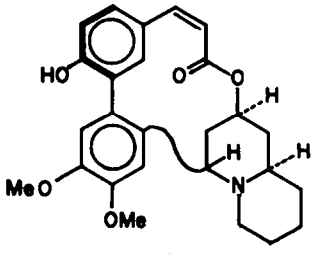
Abstract—Seco-alkaloids 4–7 were treated with VOF_3 and $VOCl_3$ under a variety of conditions. No coupled products were detected. However, ring chlorinated and side-chain oxidized products were obtained from the $VOCl_3$ oxidation of 4 and 7 respectively. The generality of the ring chlorination reaction was confirmed by chlorination of simple 0-methoxy phenols under these conditions to yield 17 and 23. In certain cases, 21 and 22, intermolecular coupling occurs in preference to chlorination.

The Type I Lythraceae alkaloids contain macrocyclic rings which include either a biphenyl (e.g. 1) or a diphenyl ether (e.g. 2).[3] These macrocycles are thought



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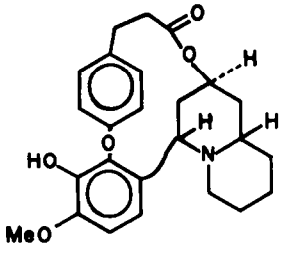

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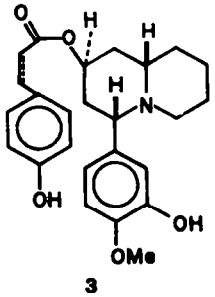
to be formed biosynthetically by the intramolecular, aryl oxidative coupling of a seco-precursor (e.g. 3).[4] Indeed, several seco-alkaloids have been found in the same plants as the macrocyclic alkaloids.[5] The apparent efficiency of nature in generating several alkaloids from a common precursor attracted our, as well as others', attention to such a sequence as a biomimetic route to these alkaloids.[6,7]



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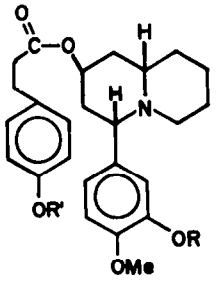
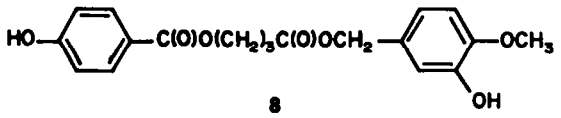
Bobbitt, *et al.*, have previously attempted to oxidize diphenol 4 with a variety of reagents.[6] In no case were alkaloids or other identified products obtained. It occurred to us that the tertiary nitrogen in 4 may have interfered with those coupling attempts. Thus, we initially attempted the intramolecular oxidative coupling of a series of diesters as models which did not contain nitrogen (e.g. 8).[8] After coupling, the four carbon bridging unit would have been removed and the coupled products incorporated into the quinolizidine portion of the alkaloids. These diesters, however, could not be induced to cyclize under a variety of oxidizing conditions.[9]

Several new oxidants[10] and new procedures for the protection of tertiary amines[11] have been introduced since Bobbitt's initial study of the oxidation of 4. Thus, a reexamination of the oxidation of 4 as well as that of the methylated derivatives 5, 6, and 7 is warranted. The



4: R = R' = H
5: R = H, R' = Me
6: R = Me, R' = H
7: R = R' = Me



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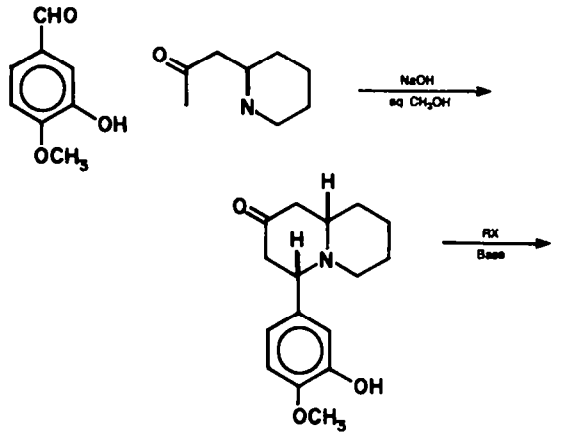
route utilized in the preparation of these substrates is outlined in the Scheme. It differs from that used previously, in that the quinolizidinone, **9**, was prepared by a



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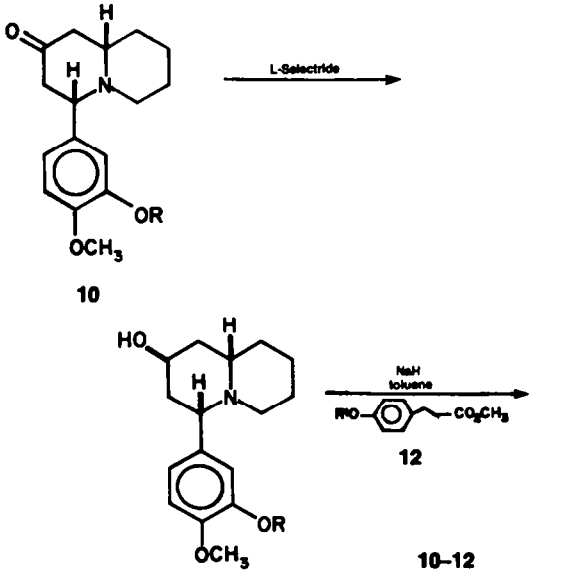
pelletierine condensation;[12] the stereoselective reduction of the ketones, **10**, was accomplished with L-selectride;[13] the MEM group was used in most cases for blocking the phenol.[14] This is a route similar to that utilized in our synthesis of abresoline.[14] In fact axial alcohol **11a**[13] was an intermediate in that synthesis and hence serves as the starting point for a detailed discussion of our present route.

Transesterification of methyl *p*-MEMoxyphenylpropionate (**12a**) with the quinolizidinol, **11a**, afforded



10

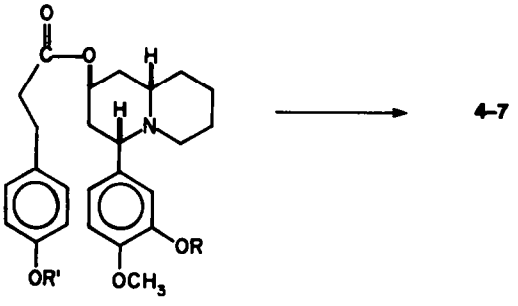
11

12

10–12

a: R = MEM
b: R = $CH_2C_6H_5$
c: R = CH_3

13a. Treatment of **13a** with trifluoroacetic acid (TFA) for 2 hr at 0°, afforded the diphenol, **4** (71% yield). If the TFA treatment was carried out for only 0.75 hr, a mixture of **4** and another product, containing one MEM group and believed to be **13b**, was obtained. Retreatment of this mixture with TFA converted **13b** into **4**. The analogous removal of the protecting group in **12a** required 1.5 hr, while deprotection of **10a** was complete within 0.5 hr. Variable amounts of an unidentified polar side-product were obtained when the deprotection of **13a** was carried out at room temperature.



13

a: R = R′ = MEM
b: R = H, R′ = MEM
c: R = R′ = $CH_2C_6H_5$
d: R = MEM, R′ = CH_3
e: R = CH_3, R′ = $CH_2C_6H_5$

The benzyl protecting group was also utilized in a synthesis of **4** in order to confirm the structure of the product from the deprotection of **13a** and in order to compare the efficiencies of the two routes. Thus, **13c**[6] was obtained from **11b** and **12b** as above. Hydrogenolysis of **13c** afforded **4** which was identical to that previously obtained. Because of the previously reported difficulties in obtaining **11b**,[13] the MEM route was found to afford better overall yields, although the removal of the benzyl groups in **13c** was found to be more reliable.

Monophenol **5** was obtained by the facile deprotection of **13d** which, in turn, was prepared from **11a** and **12c**. The other monophenol, **6**, was prepared via **13e** since the benzyl group is more easily removed than the MEM group at that isolated position. The trimethoxy derivative, **7**, was prepared directly from **11c** and **12c**.

Many attempts were made to oxidize these substrates with the common vanadium (V) oxidizing agents, VOF_3 and $VOCl_3$ and the results of these attempts are summarized in the Table. Most of these entries represent several experiments under the same or similar conditions. Those experiments in which a temperature variation is indicated were monitored by tlc (5% methanol in chloroform; silica gel) on worked-up aliquots. Only starting material was observed until the highest quoted temperatures were reached.

Borane complexes[11] and hydrochloride or perchlorate salts[15] have been utilized to protect tertiary amines during vanadium oxidations. The borane complexes of **4** and **5** were readily formed but were not stable and reverted to the amines after a short time at room temperature. Thus, in most cases, either the preformed hydrochloride or the TFA salts, generated *in situ*, were utilized.

From Table 1 it may be seen that in all cases VOF_3 afforded either recovered starting material or a tarry material which appeared as a baseline spot upon tlc. (The polar diphenol **4** had an $R_f = 0.5$ under these tlc conditions.) In spite of the fact that this reagent is a preferred one for the intramolecular coupling of monophenols

Table 1. Attempts at the oxidation of the alkaloid precursors

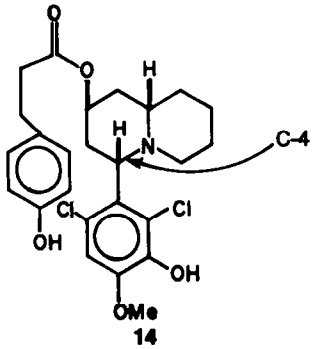
Substrate	Oxidant	Solvent	Temperature °C (Time h)	Product (% Yield)
4	VOF_3	TFA-CH_2Cl_2	-15°(2),0°,RT(1)	Polar tars
4·HCl	VOF_3	CH_2Cl_2	-78°(1),RT	Polar tars
4·ClO_4	VOF_3	CH_3CN-$CHCl_3$	-78°(2),RT(16)	Polar tars
4·BH_3	VOF_3	$CHCl_3$	-78°(1.5),RT(2)	4+Polar tars
4	$VOCl_3$	TFA-$CHCl_3$	-78°,reflux(3)	4+Polar tars
4·HCl	$VOCl_3$	CH_3CN-$CHCl_3$	-78°(1),reflux(4)	4(25)+14(13)
9	$VOCl_3$	CH_2Cl_2-TFA-TFAA	-78°(1),reflux(16)	9(20)+15(5)+16(5)
5·BH_3	VOF_3	CH_2Cl_2-EtOAc TFA-TFAA	-10°(0.5)	Polar tars
5·HCl	VOF_3	CH_2Cl_2-EtOAc TFA-TFAA	-10°(10m)	5+Polar tars
6	$VOCl_3$	CH_2Cl_2-TFA-TFAA	-78°,reflux(3)	Polar tars
7	VOF_3	CH_2Cl_2-EtOAc TFA-TFAA	-10°(0.5)	7
7	$VOCl_3$	CH_2Cl_2-TFA-TFAA	-78°(1),reflux(3)	18(70)
7	$VOCl_3$	CH_2Cl_2-TFA-TFAA	-78°,reflux(16)	18(28)+19(33)

or diethers,[16] we were unable to utilize this oxidation to give an isolable product.

When 4 was treated with $VOCl_3$ the results were slightly different. In some cases the formation of a small amount of a less polar product, 14, was observed. The mass spectrum of 14 showed ions at *m/e* 493 (M^+) and 495 ($M^+ + 2$) in the correct ratio for a dichloride. Each of the fragment ions (*m/e* 326 and 328) corresponding to the loss of the *p*-hydroxyphenylpropionate group[5] retains two chlorines. Since the aromatic region in the NMR spectrum of 14 integrated for only five protons, we concluded that the substitution had occurred in the aromatic ring of the quinolizidine portion of the molecule. The assigned position of the halogens in 14 is based on the observation that the C-4 proton of 14 has a downfield resonance (δ 4.27) compared to its position in the spectrum of 4 (δ 3.4) and by analogy with the substitution patterns observed in the following model studies.

Vanadium oxytrichloride treatment of quinolizidinone 9, a model for the nitrogen containing portion of 4, afforded a monochlorinated product, 15, as well as another dichloro compound, 16. The structural assignment of 15 is based on the NMR spectrum which displayed a two-proton, AB quartet at δ 6.67 indicative of ortho coupled protons. The C-4 proton resonance of 16 is further downfield (δ 4.2) than that of 15 (δ 3.8) indicating the presence of an additional deshielding polar group near that proton. Our assignment of structure 16 with the chlorines *ortho* and *para* to the OH group is also justified by the observation, noted below, that only monosubstitution occurs when the *para* position is blocked.

Methyl *p*-hydroxyphenylpropionate, a model for the other aryl ring in 4, was recovered unchanged from treatment with $VOCl_3$. Methyl dihydroferulate, however, afforded the monochlorinated product 17. Thus, the



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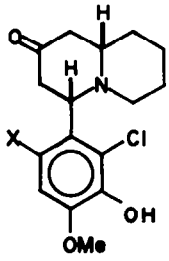
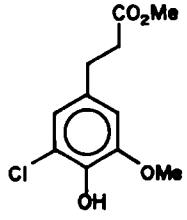


15: X = H
16: X = Cl

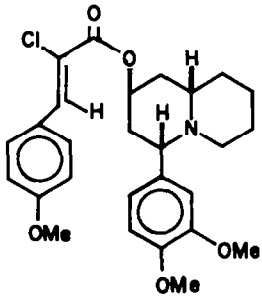


17

presence of an *o*-methoxyphenol appears to be critical for this chlorination reaction. Schwartz *et al.* have also noted that chlorination is a side reaction to coupling when this structural unit is involved.[17] In the case of **4**, chlorination is the *only* reaction occurring.

Since monophenol **5** is also an *o*-methoxyphenol, we did not attempt its oxidation with $VOCl_3$, and the other monophenol, **6**, afforded only polar tars. The trimethoxy analogue, **7**, however, afforded the unusual side-chain chlorination and oxidation products, **18** and **19**. These products were identified by their NMR and mass spectra as discussed in a previous communication.[18] In this case the $VOCl_3$ appears to be functioning as a Cl_2 equivalent.

Following the observation of these chlorinations and the lack of coupling of these seco-alkaloids and models, we studied even simpler compounds under these conditions. Thus, the toluene derivatives **20–22** were subjected to this treatment as models for the tri-substituted



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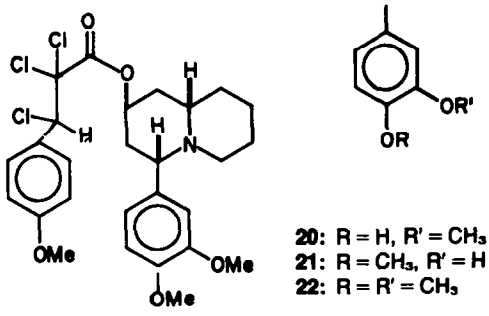
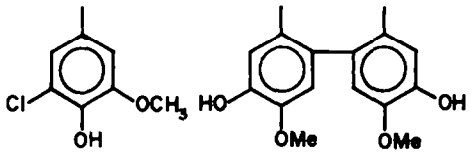


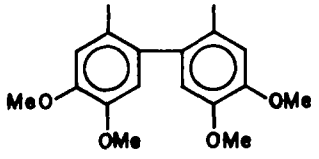
19

20: R = H, R' = CH_3
21: R = CH_3, R' = H
22: R = R' = CH_3

benzene rings of the seco-alkaloids. As expected, treatment of creosol (**20**) with $VOCl_3$ afforded 5-chlorocreosol (**23**) which was identified by comparison with an authentic sample.[19] Surprisingly, however, **21** and **22** afforded the biphenyls, **24** and **25** respectively, in excellent yields. These were the first products of oxidative coupling found in the study![20] The structure of **25** was confirmed by comparison of its m.p. with that previously recorded.[21] However, there was considerable discrepancy between the m.p. of **24** (157–8°) and that reported (192–4°).[22] Therefore, the structure of **24** was confirmed by conversion to **25** by diazomethane treatment. Furthermore, oxidation of **21** with $K_3Fe(CN)_6$ afforded a sample of **24** with the same melting range as before. Oxidation of **21** with benzoylperoxide[22] afforded a low yield of a mixture of products, the major one (3% yield) of which had an NMR spectrum similar to that of our sample. However, we were unable to crystallize this sample. Our sample of **24** afforded a dibenzoate whose m.p. corresponded to that reported.[22] Thus, **24** must indeed have the structure assigned. The m.p. discrepancy remains unresolved.



23 **24**



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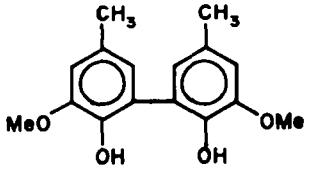
The biphenyls **24** and **25** were also obtained when **21** and **22** were treated with VOF_3.[23] Treatment of **20** with VOF_3 afforded at least two unidentified products neither of which was the biphenyl **26**. A sample of **26** was prepared, for comparison, from **20** by oxidation with $K_3Fe(CN)_6$.[24]



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CONCLUSION

In addition to the work of Schwartz, *et al.*[17] there is one other report of a ring chlorination with $VOCl_3$.[20b] In this case substantial yields of ring chlorination products were obtained when *o*-allylphenols were treated with $VOCl_3$ at −78° in ether. Substitution at the *para* position appeared to be the initial mode of attack especially when that position already held a t-Bu group. In our case, the chlorination competes with coupling when there is an *o*-OMe group and the latter pathway is restricted by the presence of a *para*-substituent (i.e. **17** and **20**) or by other factors (**4** and **9**). In addition, we find *ortho*-chlorination to be the initial process. It appears that various mechanistic pathways are in operation including those which would accomodate the side chain oxidations observed with **7**. Hence to advance a mechanism at present without further experimentation would be too speculative.

A final conclusion which we may draw from this work is that the intramolecular coupling of the seco-alkaloids by these vanadium (V) reagents is sluggish, if at all possible. This may be the result of some deactivation (electronic or steric) of the aryl by the quinolizidine ring since **9** could not be coupled or of the inherent difficulty in cyclizing to a 12-membered ring. It is likely that the successful synthesis of Lythraceae alkaloids by this route will depend upon the employment of some sort of template to hold the aryl groups in the proper orientation for coupling.

EXPERIMENTAL[25]

Methyl 3-(p-MEMoxyphenyl)propionate (**12a**)

A soln of methyl 3-(*p*-hydroxyphenyl)propionate (7 g; 39 mmole) in toluene (25 ml) was added dropwise to a stirred

suspension of sodium hydride (2 g; 42 mmole) in toluene (50 ml). After refluxing for 30 min this mixture was cooled to 0° and 4.5 ml (39 mmole) of methoxyethoxymethyl chloride (MEMCl) was added dropwise. After 4 hr at room temp the soln was diluted with water and extracted with benzene. The organic layer was washed with NaOHaq and water then dried (Na_2SO_4) and concentrated. Chromatography of the residue [silica gel; hexane:benzene (1:1)] afforded **12a** (5 g; 48%). Further elution (benzene:EtOAc) afforded slightly impure **12a** (1.6 g). IR (film) 1735, cm^{-1}; NMR ($CDCl_3$) δ 2.73 (m, 4H, $-CH_2CH_2C(O)-$), 3.33 (s, 3H, OCH_3), 3.62 (s, 3H, $C(O)OCH_3$), 5.20 (s, 2H, $-OCH_2O-$), 7.00 (AB quartet, 4H, aryl).

2 - (p - *MEMoxyphenylpropionoyloxy*) (*a*) - 4 - (3' - *MEMoxy* - 4' - *methoxyphenyl*) (*e*) - trans - *quinolizidine* (**13a**)

A soln of **11a**[13] (3.65 g; 10 mmole) and **12a** (2.5 g; 9.3 mmole) in 80 ml xylene was refluxed for 1 hr under a Dean-Stark trap. About 25 mg of sodium hydride (50% dispersion in oil) was added and the refluxing was continued for 6 hr. The cooled mixture was diluted with benzene (100 ml), washed with water and $NaHCO_3$aq, and dried (Na_2SO_4). Concentration of this soln *in vacuo* afforded an oil (6 g) which was subjected to column chromatography. Elution with benzene-MeOH (19:1) afforded 4.5 g (81%) of pure **13a** as a viscous oil. IR (film) 1725, 1510, 1100 cm^{-1}; NMR ($CDCl_3$) δ 2.80 (m, 2H, $C(O)CH_2CH_2Ar$), 3.30 (s, 6H, 2x CH_2OCH_3), 3.80 (s, 3H, $ArOCH_3$), 5.0 (6r, 1H, >CH–O–C(O)), 5.17 and 5.27 (s, 2H each, 2x $-O-CH_2O-$), 6.7–7.2 (m, 7H, aryl); MS *m/e* 601 (M^+), 512 (M^+-MEM), 348 and 346 (M^+-ester), 60 (Base). (Found: C, 66.05; H, 8.05; N, 2.28. Calcd. for $C_{33}H_{47}NO_9$: C, 65.87; H, 7.87; N, 2.33%.)

2 - (p - *Hydroxyphenylpropionyloxy*) (*a*) - 4 - (3' - *hydroxy* - 4' - *methoxyphenyl*) (*e*) - trans - *quinolizidine* (**4**)

Trifluoroacetic acid (TFA) (10 ml) was added dropwise to a 0° soln of **13a** (0.5 g; 0.83 mmole) in 15 ml CH_2Cl_2. After stirring at 0° for 2 hr the mixture was diluted with water and neutralized with $NaHCO_3$aq. The mixture was extracted with $CHCl_3$ and the organic layers dried and concentrated *in vacuo*. The resulting oil was purified by column chromatography [C_6H_6:MeOH (95:5)] to afford 0.25 g (71% yield) of **4**[6]: IR (film) 3400 (br), 1725, 1515 cm^{-1}; NMR ($CDCl_3$) δ 2.76 (m, 4H, $C(O)CH_2CH_2Ar$), 3.80 (s, 3H, $-OCH_3$), 5.0 (br, 1H, >CH–O–C(O)), 5.93 (brs, 2H, 2x OH), 6.6–7.2 (m, 7H, aryl); MS (*m/e*) 425 (M^+, base), 260 and 258 (M^+-ester).

2 - (p - *Methoxyphenylpropionoyloxy* (*a*) - 4 - (3' - *MEMoxy* - 4' - *methoxyphenyl*) (*e*) - trans - *quinolizidine* (**13d**)

From the treatment of **11a** (3 g; 8.2 mmole) with **12c**[26] (1.6 g; 8.2 mmole) as in the preparation of **13a**, **13d** (3.6 g; 83%) was obtained as a gum: IR (film) 1725, 1510, 1100 cm^{-1}; NMR ($CDCl_3$) δ 2.8 (m, 4H), 3.27 (s, 3H), 3.67 (s, 3H), 3.84 (s, 3H), 5.0 (br, 1H), 5.20 (s, 2H), 6.6–7.2 (m, 7H); MS (*m/e*), 527 (M^+; base), 348 and 346 (M^+-ester). (Found: C, 68.14; H, 8.04; N, 2.63. Calcd. for $C_{30}H_{41}NO_7$: C, 68.29; H, 7.83; N, 2.65%.)

2(p - *Methoxyphenylpropionoyloxy*) (*a*) - 4 - (3' - *hydroxy* - 4 - *methoxyphenyl*) (*e*) - trans - *quinolizidine* (**5**)

From the treatment of **13d** (2.8 g; 5.3 mmole) with TFA as above **5** (1.85 g; 80%) was obtained, after chromatography: IR (film) 3450 (br), 1725, 1515 cm^{-1}; NMR ($CDCl_3$) δ 2.8 (m, 4H), 3.85 (s, 3H), 3.80 (s, 3H), 5.0 (br, 1H), 6.1 (brs, 1H, OH), 6.6–7.1 (m, 7H); MS (*m/e*), 439 (M^+), 260 and 258 (M^+-ester), 172 (base). *Exact mass*. Calcd. for $C_{26}H_{33}NO_5$: 439.2359; Meas. 439.2396.

2 - (p - *Benzyloxyphenylpropionoyloxy*) (*a*) - 4 - (3',4' - *dimethoxyphenyl*) (*e*) - trans - *quinolizidine* (**13e**)

From the treatment of **11c**[13] (0.40 g; 1.4 mmole) and **12b**[6] (0.38 g; 1.4 mmole) as in the preparation of **13a**, **13e** (0.45 g; 61%) was obtained as an oil: IR (film) 1730, 1510 cm^{-1}; NMR ($CDCl_3$) δ 2.8 (m, 4H), 3.77 (s, 3H), 3.83 (s, 3H), 4.97 (s and br m, 3H, $-OCH_2-Ar$ and >CH–O–C(O)), 6.7–7.2 (m, 7H), 7.30 (s, 5H).

2 - (p - *Hydroxyphenylpropionoyloxy*) (*a*) - 4 - (3',4' - *dimethoxyphenyl*) (*e*) - trans - *quinolizidine* (**6**)

The benzyl ether **13e** (0.3 g; 0.57 mmole) was hydrogenated in EtOH over 10% Pd–C (20 mg). Filtration and concentration *in vacuo* afforded an oil which was purified by preparative tlc [$CHCl_3$:MeOH (19:1)] and recrystallization ($CHCl_3$-benzene) to yield **6** (0.16 g; 64%); m.p. 168–70°; IR (KBr) 3250, 1725, 1515 cm^{-1}; NMR ($CDCl_3$) 2.8 (m, 4H), 3.83, 3.88 (2s, 6H), 5.07 (br, 1H), 6.7–7.2 (m, 7H); MS (*m/e*) 429 (M^+), 274 and 272 (M^+-ester), 191 (Base); *Exact mass*. Calcd. for $C_{26}H_{33}NO_5$: 439.2359; Meas. 439.2382.

2 - (p - *Methoxyphenylpropionoyloxy*) (*a*) - 4 - (3',4' - *dimethoxyphenyl*) (*e*) - trans - *quinolizidine* (**7**)

From the treatment of **11c**[13] (0.75 g; 2.6 mmole) with **12**[26] (0.50 g; 2.6 mmole) as in the preparation of **13a** oily **7** (0.88 g; 75%) was obtained: IR (film) 1725, 1515 cm^{-1}; NMR ($CDCl_3$) δ 2.8 (m, 4H), 3.75, 3.83, 3.87 (3s, 9H), 5.0 (m, 1H), 6.7–7.2 (m, 7H); MS (*m/e*) 453 (M^+), 274 and 272 (M^+-ester), 169 (Base). (Found: C, 71.51; H, 7.86; N, 2.93. Calcd. for $C_{27}H_{33}NO_5$: C, 71.48; H, 7.78; N, 3.09%.)

General procedures for oxidations with VOF_3

(A)[27] A soln consisting 0.23 mmole of substrate in 20 ml CH_2Cl_2 and 5 ml TFA was cooled to −15° and treated with 50 mg (0.4 mmole) of VOF_3. After stirring at an appropriate temp for a period of time (Table) the mixture was poured into a 10% citric acid soln and basified with NH_4OH. Extraction with $CHCl_3$ and removal of the solvent afforded the crude product. Aliquots taken during the reaction were worked up in the same manner.

(B)[16] A soln of 0.23 mmole of the substrate in 25 ml CH_2Cl_2, 5 ml TFA, and 5 drops TFA anhydride (TFAA) was cooled to −10° under a N_2 and treated with a soln of VOF_3 (60 mg; 0.5 mmole) in the minimum amount of EtOAc. The mixture was stirred for 30 min and quenched by the addition of 10% citric acid soln. Basification with NH_4OH, extraction with $CHCl_3$ and removal of the solvent afforded the crude product.

Oxidation of diphenol **4** *with* $VOCl_3$

Isolation of **14**. An ether soln of **4** (100 mg; 0.23 mmole) was treated with gaseous HCl and resulting ppt was removed by filtration and washed with ether. A soln of this hydrochloride salt in 20 ml acetonitrile and 5 ml $CHCl_3$ was cooled to −78° and treated with 100 μl (1 mmole) $VOCl_3$ under N_2. After 1 hr the cooling bath was removed and the mixture refluxed for 4 hr. The cooled mixture was treated with $NaHCO_3$aq, extracted with $CHCl_3$, and the organic layer dried (Na_2SO_4) and concentrated in *vacuo*. Preparative tlc of the crude product (silica gel; 5% MeOH:$CHCl_3$) afforded **14** (15 mg; 13%): IR (film) 3400, 1725 cm^{-1}; NMR ($CDCl_3$) δ 2.8 (m, 4H), 3.88 (s, 3H), 4.27 (d of d, J_1 = 12 Hz, J_2 = 3 Hz, 1H, C_4–H), 5.1 (br, 1H), 6.7–7.3 (m, 5H); MS (*m/e*) 493 (M^+), 495 (M^+-2, 80% of M^+), 328 and 326 (M^+-ester), 149 (Base); *Exact mass*. Calcd. for $C_{25}H_{29}Cl_2NO_5$: 493.1423; Meas. 493.1414.

Oxidation of **9** *with* $VOCl_3$

Isolation of **15** and **16**. To a soln of **9** (0.50 g; 1.8 mmole) in 50 ml of CH_2Cl_2 containing 10 ml of TFA and 5 drops of TFAA at −78° under N_2 was added 250 μl (2.5 mmole) of $VOCl_3$. After 1 hr the cooling bath was removed and the mixture was refluxed overnight. After work-up as before a crude product was obtained which contained, by tlc analysis, **9** and minor amounts of two less polar materials. Separation by tlc afforded 25 mg (5%) of the more polar of these two products, **15**: NMR ($CDCl_3$) δ 3.8 (m, 1H, C_4–H), 3.87 (s, 3H), 6.97 (ABq, J = 9 Hz, 2H); MS (*m/e*) 309 (M^+), 311 (M^+ + 2; 35% M^+), 184 (base); *Exact mass*. Calcd. for $C_{16}H_{20}ClNO_3$: 309.132; Meas.: 309.1110.

Of the other product, **16**, 30 mg (5%) was obtained: m.p. 129–31° ($CHCl_3$–C_6H_{14}); IR (KBr) 3400 (br), 1710, 750 cm^{-1}; NMR ($CDCl_3$) δ 3.87 (s, 3H), 4.23 (d of d, J_1 = 12 Hz, J_2 = 4 Hz, 1H, C_4–H), 6.78 (s, 1H, aryl); MS (*m/e*) 343 (M^+), 345 (M^+ + 2; 60% M^+), 110 (Base); *Exact mass*. Calcd. for $C_{16}H_{19}Cl_2NO_3$: 343.0742; Meas.: 343.0754.

Oxidation of methyl dihydroferulate with $VOCl_3$

Isolation of **17**. To a soln of methyl dihydroferulate[28] (0.20 g; 0.95 mmole) in 20 ml CH_2Cl_2, containing 2 ml TFA and 2 drops TFAA at −78° was added 200 μl (2 mmole) of $VOCl_3$. After 1 hr the cooling bath was removed and the soln refluxed for 3 hr. After the normal workup and purification of the crude product by bulb-to-bulb distillation, **17** (0.17 g; 73%) was obtained: IR (film) 3450 (br), 1735 cm^{-1}; NMR ($CDCl_3$) δ 2.7 (m, 2H), 3.62 (s, 3H), 3.78 (s, 3H), 6.07 (s, 1H, –OH), 6.57–6.72 (2d, J ≈ 2 Hz, 2x 1H, aryl); MS (*m/e*) 244 (M^+), 246 (M^+ + 2), 151 (Base); *Exact mass.* Calcd. for $C_{11}H_{13}ClO_4$: 244.0502; Meas.: 244.0520.

Oxidation of **7** *with* $VOCl_3$

Isolation of **18** and **19**. A soln of **7** (100 mg; 0.22 mmole) was treated with $VOCl_3$ (100 μl; 1.0 mmole) as above. After refluxing overnight the mixture was worked up as usual. Preparative tlc (4% MeOH–$CHCl_3$) afforded two new compounds both of which were less polar than **7**. The more polar of these was **18** (30 mg; 28%): IR (film) 1710, 1600, 760 cm^{-1}; NMR ($CDCl_3$) δ 3.83 (s, ~6H), 3.85 (s, ~3H), 5.2 (br, 1H), 6.8 (m, 5H), 7.84 (d, J = 9 Hz, ~2H, aryl), 7.86 (s, ~1H, C(O)CCl=CH–); MS (*m/e*) 485 (M^+), 487 (M^+ + 2; 43% M^+), 450 (M^+–Cl), 274 and 272 (M^+-ester), 191 (Base); *Exact mass.* Calcd. for $C_{27}H_{32}ClNO_5$: 485.1969; Meas.: 495.1955.

The less polar product was **19** (40 mg; 33%): IR (film) 1740, 1615, 760 cm^{-1}; NMR ($CDCl_3$) δ 3.80, 3.83, 3.85 (3s, 9H), 5.2 (br, 1H), 5.68 (s, 1H, C(O)–CCl_2CHCl–), 6.9 (m, 5H), 7.53 (d, J = 9 Hz, 2H); MS (*m/e*) 555 (M^+), 557 (M^+ + 2; 90% M+), 559 (M^+ + 4; 40% M^+), 485 (M^+-2Cl), 450 (M^+-3Cl), 274 and 272 (M^+-ester), 191 (Base); *Exact mass.* Calcd. for $C_{27}H_{32}Cl_3NO_5$: 555.1346; Meas.: 555.1386.

Oxidation of creosol (**19**) *with* $VOCl_3$

Treatment of creosol[29] (0.20 g; 1.5 mmole) with $VOCl_3$ as above with refluxing overnight, work up as usual, and filtration of a benzene soln of the mixture through silica gel afforded **22**[19] (0.12 g; 48%). An analytical sample was prepared by bulb-to-bulb distillation. The spectra and the tlc behavior of this sample were identical with those of an authentic sample. NMR ($CDCl_3$) δ 2.23 (s, 3H), 3.80 (s, 3H), 5.6 (br, 1H), 6.48 (d, J = 2 Hz, 1H), 6.67 (d, J = 2 Hz, 1H). (Found: C, 55.44; H, 5.45. Calcd. for $C_8H_9ClO_2$: C, 55.67; H, 5.25%.)

4,4'-Dihydroxy-5,5'-dimethoxy-2,2'-dimethylbiphenyl (**23**).

(A) Treatment of **20**[30] (200 mg; 1.5 mmole) with $VOCl_3$ as before (room temp for 3 hr) and the usual work up, followed by recrystallization (hexane–benzene) of the crude product afforded **23** (170 mg; 83%): m.p. 157–58° (lit.: 192–94°);[22] NMR ($CDCl_3$) δ 1.95 (s, 3H), 3.80 (s, 3H), 5.65 (s, 2H), 6.57 (s, 2H), 6.77 (s, 2H). (Found: C, 70.14; H, 6.32. Calcd. for $C_{16}H_{18}O_4$: C, 70.06; H, 6.57%.) Schotten–Baumann benzoylation yielded 4,4'-dibenzoyloxy-5,5'-dimethoxy-2,2'-dimethylbiphenyl: m.p. 260–61° (lit.: 257°).[22]

(B) Treatment of **20** (330 mg; 2.4 mmole) with VOF_3 (Method B) for 20 min at −10° afforded **23** (300 mg; 91%).

(C) Treatment of **20** (150 mg; 1.1 mmole) with $K_3Fe(CN)_6$ (0.72 g) in the manner described[24] afforded **23** (65 mg; 44%).

(D) Treatment of a benzene soln containing **20** (335 mg) with benzoyl peroxide (1 g) for 3 hr at 50°, followed by work up as described[22] afforded 24 mg of a mixture of products. The principal fraction (10 mg) from the preparative tlc of this sample had the same tlc behavior and NMR behavior (including C_6D_6 solvent shifts) as the samples of **23** obtained by methods A–C.

2,2'-Dimethyl-4,4',5,5'-tetramethoxybiphenyl (**24**)

(A) Treatment of **21** (200 mg; 1.3 mmole) with $VOCl_3$ as above (refluxed for 2 hr) afforded, after recrystallization from $CHCl_3$–benzene, **24** (160 mg; 81%): m.p. 117–8° (lit.: 115–6°);[30] NMR ($CDCl_3$) δ 1.87 (s, 6H), 3.67 (s, 6H), 3.75 (s, 2H), 6.60 (s, 2H. (Found: C, 71.89; H, 7.39. Calcd. for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33%.)

(B) Treatment of **21** (200 mg)with VOF_3 (Method B) for 15 min afforded **24** (160 mg; 81%).

(C) A soln of **23** (100 mg; 0.36 mmole) in CH_2Cl_2–MeOH (3:1) was treated with excess diazomethane overnight. After quenching with a few drops of AcOH, the solvent was removed to afford **24** (70 mg; 63%) identical with that previously obtained.

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REFERENCES

[1]Other papers in this series: I, J. Quick and R. Oterson, *Tetrahedron Letters* 745 (1977); II, Ref. 8*a*; III, Ref. 8*b*; IV, Ref. 3*a*; V, Ref. 14; VI, Ref. 12; VII, Ref. 18; VIII, Ref. 13.

[2]Presented in part at the Northeast Regional Meeting, ACS, Boston, MA, June 1978, Abstract ORGN 35.

[3a]J. Quick, C. Mondello, M. Humora and T. Brennan, *J. Org. Chem.* **43**, 2705 (1978) and refs therein; [b]For a different system of classification see: K. Fuji, T. Yamada, E. Fujita and H. Murata, *Chem. Pharm. Bull.* **26**, 2515 (1978).

[4]J. P. Ferris, C. B. Boyce and R. C. Briner, *Tetrahedron Letters* 5129 (1966).

[5]A. Rother and A. E. Schwarting, *Phytochemistry* **17**, 305 (1978).

[6]J. P. Rosazza, J. M. Bobbitt and A. E. Schwarting, *J. Org. Chem.* **35**, 2564 (1970).

[7]J. T. Wrobel and M. Golebiewski, *Rocz. Chem.* **45**, 705 (1971).

[8a]J. Quick and J. K. Crelling, *J. Org. Chem.* **43**, 155 (1978); [b]*Syn. Comm.* **8**, 181 (1978).

[9]J. K. Crelling, unpublished results.

[10]See for example: S. M. Kupchan and A. Liepa, *J. Am. Chem. Soc.* **95**, 4062 (1973); M. Schwartz and I. Mami, *Ibid.* **97**, 1239 (1975); S. Tobinaga, *Bioorg. Chem.* **4**, 110 (1975).

[11]M. Schwartz, B. Rose and B. Vishnurajjala, *J. Am. Chem. Soc.* **95**, 612 (1973).

[12]J. Quick and C. Meltz, *J. Org. Chem.* **44**, 573 (1979).

[13]J. Quick, C. Meltz and R. R. Ramachandra, *OPPI* **11**, 111 (1979).

[14]J. Quick and R. Ramachandra, *Syn. Comm.* **8**, 511 (1978).

[15]M. A. Schwartz, private communication.

[16]S. M. Kupchan, O. P. Dhingra and C.-K. Kim, *J. Org. Chem.* **43**, 4076 (1978) and refs therein.

[17]M. A. Schwartz, B. F. Rose, R. A. Halton, S. W. Scott and B. Vishnurajjala, *J. Am. Chem. Soc.* **99**, 2571 (1977).

[18]J. Quick and R. Ramachandra, *Tetrahedron Letters* 709 (1979).

[19]J. M. Gess and C. W. Dence, *Tappi* **54**, 1114 (1971).

[20]Low yields of biphenyls have been previously obtained via the intermolecular coupling of phenols by $VOCl_3$: [a]W. L. Carrick, G. L. Karapinka and G. T. Kwiatkowski, *J. Org. Chem.* **34**, 2388 (1969); [b]D. T. Dalgleish, N. P. Forrest, D. C. Nonhebel and P. L. Pauson, *J. Chem. Soc.* Perkin 1, 584 (1977).

[21]R. Cromartie, J. Harley-Mason and D. Wannigama, *Ibid.* 1982 (1958).

[22]R. B. Roy and G. A. Swan, *Ibid.*, (C), 83 (1968).

[23]An intermolecular coupling of an arylether with VOF_3 has been recently reported: F. R. Hawgill, *Tetrahedron* **34**, 1595 (1978).

[24]C. G. Haynes, A. H. Turner and W. A. Waters, *J. Chem. Soc.* 2823 (1956).

[25]For general experimental information see Ref. 3*a*.

[26]H. O. House and J. K. Larson, *J. Org. Chem.* **33**, 448 (1968).

[27]S. M. Kupchan, A. J. Leipa, V. Kameswaran and R. F. Bryan, *J. Am. Chem. Soc.* **95**, 6861 (1973).

[28]T. Strukov and O. A. Kolganova, *Z. Obshchei. Khim.* **29**, 3831 (1959); *Chem. Abstr.* **54**, 19675h (1960).

[29]A. Arcoleo and T. Garofano, *Ann. Chim. Rome* **47**, 1142 (1957); *Chem. Abstr.* **52**, 6300e (1958).

[30]E. Fedeli, A. Feicchi and G. Jommi, *Gaz. Chim. Ital.* **89**, 824 (1959); *Chem. Abstr.* **54**, 22455e (1960).