because the *ortho* aromatic protons of some compounds are found several cps (15–40) upfield with respect to the other (*meta* and *para*) protons.

In fact, when the shielded *ortho* protons belong to 1,2-disubstituted central ring—i.e., Table V: compounds 3–5—the four central nuclear protons show the characteristic pattern of the A_2B_2 system and $\Delta\nu/J$ values were then estimated according to standard procedures (*8*).

In another case, when the shielded *ortho* protons belong to a 1,2-disubstituted side ring—i.e., Table I: compounds 4, 8–10—they appear shifted upfield in the spectrum.

As far as the assignments of methyl signals are concerned, they were usually assigned on the basis of the relative peak intensities. Where this criterion proved insufficient because of the presence of peaks of equal intensity, opportune correlation maps were built up using, as references, compounds in which methyl peaks were unequivocally assigned.

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Synthesis of Biphenyl Portion of Decinine

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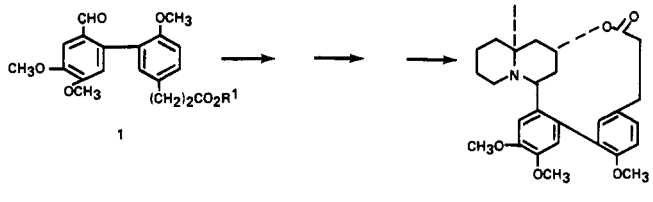
The syntheses and characterization of intermediates leading to 3-[3-(2-formyl-4,5-dimethoxyphenyl)-4-methoxyphenyl] propionic acid (1a), a possible precursor in the total synthesis of decinine methyl ether, are described.

The Lythraceae alkaloids have been of continuing interest to our laboratories—first, as problems in structure determination (*10, 11, 14, 37*) and, more recently, as structures with possible medicinal utility as anti-inflammatory (*25*) and diuretic agents (*36*).

In recent years (*3, 10, 14, 16, 17, 21, 37*), not only have the structures of several of these quinolizidine alkaloids been elucidated, but Ferris et al. (*15*) have proposed a possible biogenetic route for their syntheses. Subsequently, Matsunaga et al. (*26*) demonstrated the chemical feasibility of forming 2-oxo-4-quinolizidines from benzaldehyde and isopelletierine. Recently, Rosazza et al. (*31*) described a synthesis of Lythraceae alkaloids which required only a convenient method for forming the biphenyl linkage found in several members of this family of alkaloids—e.g., decinine, 2—in order to be considered a total synthesis. Therefore, the preparation of biphenyls—e.g., 1—containing substituents which could be used in the preparation of decinine, 2 is described.



1

The synthesis of 1 was undertaken as shown in Chart I. The intermediates used in this synthesis are new, and are listed in Table I, together with appropriate physical constants.

3,4-Dimethoxyphenylacetone was prepared from 3,4-dimethoxyphenylacetic acid and acetic anhydride. In our hands, attempts to prepare the acetone from 3,4-dimethoxyphenylacetonitrile via the acetoacetonitrile (*33*) led chiefly to the recovery of unchanged dimethoxyphenylacetoacetonitrile. Ring closure of the acetone with nitromalondialdehyde (*13*), to give 3, was effected in aqueous base (*4, 6, 22–24*). Etherification to give the methyl ether,

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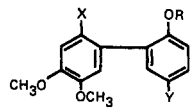
Table I. Substituted Biphenyls



Compd.[a]	R	X	Y	Mp, °C[b]	Yield, %	Solvent[c]
1a	CH_3	CHO	$(CH_2)_2CO_2H$	127–128	25	4–7
3	H	H	NO_2	196–198	87	1
4a	CH_3	H	NO_2	119–120	78	2–3
b	$CH_2C_6H_5$	H	NO_2	136–138	98	4–5
5a	CH_3	H	NH_2	84–88	56	6–3
b	$CH_2C_6H_5$	H	NH_2	113–115	81	4–7
6a	CH_3	H	$CH=CHCO_2H$	230–232	64	5–4
b	$CH_2C_6H_5$	H	$CH=CHCO_2H$	212–214	26	8
7a	CH_3	H	CN	118–119	55	9
b	$CH_2C_6H_5$	H	CN	144–146	20	4
8a	CH_3	H	CHO	109–110	45	4
b	$CH_2C_6H_5$[d]	H	CHO	79–81	27	10
9a	CH_3	H	$(CH_2)_2CO_2H$	155–156	98	4–7
b	CH_3	H	$(CH_2)_2CO_2CH_3$	58–60	90	9–7
10a	CH_3	CH_2Cl	$(CH_2)_2CO_2H$	150–152	28	6–11
b	CH_3	CH_2Cl	$(CH_2)_2CO_2CH_3$	92–94	30	12

[a] Elemental analyses (C, H, N) in agreement with theoretical values have been obtained and submitted for review. [b] Melting points were taken in a Thomas-Hoover capillary melting point apparatus and are corrected. [c] 1. Toluene, 2. carbon tetrachloride, 3. ligroin, 4. ethanol, 5. ethyl acetate, 6. benzene, 7. water, 8. acetonitrile, 9. methanol, 10. petroleum ether (bp 90° to 110° C), 11. hexane, 12. ether. [d] Semicarbazone, mp 182–84° C (ethanol).

4a, was accomplished equally well with methyl iodide in alcoholic potassium hydroxide, or in dimethylformamide containing potassium carbonate. The benzyl ether, 4b, was formed using benzyl bromide in dimethylformamide-carbonate. Reduction to the amino ether, 5a, was performed catalytically, using palladium on charcoal, or chemically using hydrazine and Raney nickel (*5*). The latter procedure was used to prepare 5b.

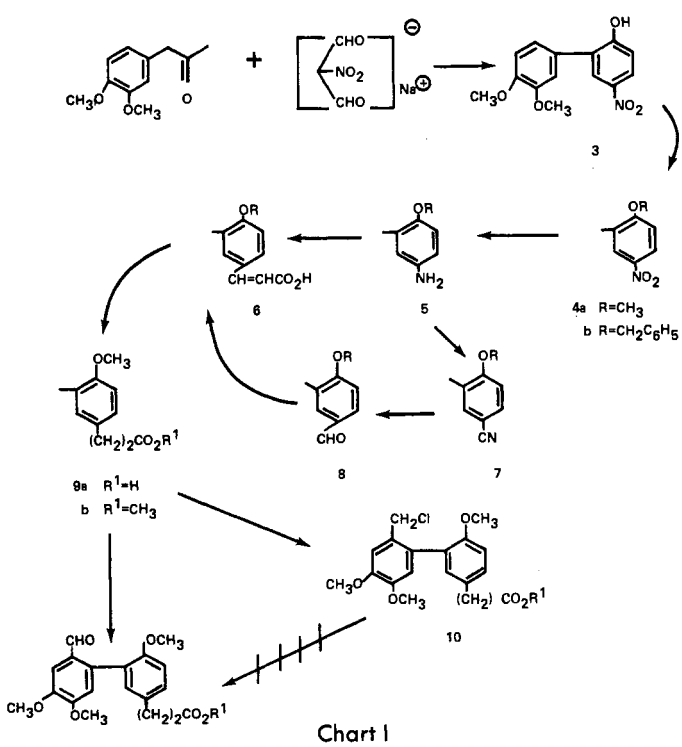
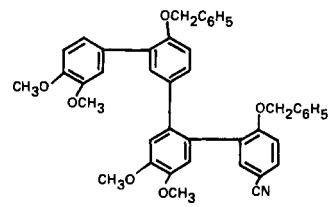


Chart I

Repeated attempts to prepare 6a and b, using the Meerwein reaction (*9, 30*), produced only trace amounts of acidic materials after appropriate hydrolysis and extraction. This was in contrast to the 60% yield of crude *p*-benzyloxycinnamic acid obtained in a model reaction. In light of these results, the longer sequence 5 → 7 → 8 → 6 was undertaken.

The conversion of 5b to 7b proceeded with a 20–30% yield of crystalline 7b obtained only after chromatography. In addition to 7b, a second compound was isolated in low yield during the chromatography. Mass spectral data on this material showed a molecular ion of 663 and numerous fragments resulting from the loss of the tropylium ion (−91). The infrared spectrum showed that the material was a nitrile, while the nmr spectrum indicated protons in the following ratios—aromatic–21, CH_3O–12; $C_6H_5CH_2O$–4. The ultraviolet data were consistent with a tetraphenyl system, while the thin-layer chromatographic findings showed a major component with several minor impurities. A likely structure for the major component is shown.



A similar reaction with 5a gave a 50–60% yield of 7a, although chromatography was again required for purification.

The conversions of 7a and b to the aldehydes 8a and b were unsuccessful under the conditions of the Stephen reaction (*27, 34*). When 7b was treated with triethoxyaluminohydride (*8*), a mixture of 7b and 8b was obtained. Unchanged 7b could be recovered readily by treating the mixture with malonic acid and separating 7b from the acidic product, 6b. The catalytic reduction of 7b in the presence of semicarbazide gave 8b semicarbazone (*20*) which, on hydrolysis in the presence of formaldehyde, led to pure 8b.

In 1-gram runs, 7a could be converted cleanly to 8a with triethoxyaluminohydride. Larger runs were less clean-cut, and unreacted 7a was recovered after the reaction of the mixture with malonic acid. The conversion of 8a and b to the cinnamic acids 6a and b, the reduction of 8a in aqueous potassium hydroxide to the propionic acid

9a, and the esterification of 9a to 9b proceeded readily, and in good yields. The chloromethylation of 9a and b with chloromethylmethyl ether (*12*) or paraformaldehyde and hydrogen chloride (*7, 29*) gave poor yields of the solid chloromethyl derivatives 10a and b. Completion of the Sommelet reaction (*2*) did not lead to the isolation of any aldehyde. The Gattermann synthesis for aromatic aldehydes also was not useful (*1, 18, 19, 35*).

However, under the conditions of the Vilsmeier reaction (*32*), 9a did yield 1b as an oil. The oil appeared homogeneous in several thin-layer systems but gave unsatisfactory elemental analyses. Hydrolysis of 1b gave a crystalline acid, 1a, which analyzed satisfactorily and which had a spectra seemingly consistent with its structure. Reesterification of 1a with methanol and hydrogen chloride gave what appeared to be an acetal ester which could not be selectively hydrolyzed to 1b.

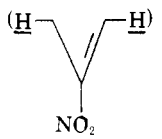
Spectral studies with 1a and b did not allow us to conclusively assign the position of the formyl group. However, it has been stated that appreciable yields of aldehyde are obtained in the Vilsmeier reaction only when a position para to the aromatic activating groups is available (*28*). The structure of 1a is also the structure one would predict on the basis of current theories dealing with aromatic substitution.

EXPERIMENTAL

Elemental, uv, and nmr spectral analyses were performed by members of the staff of the Analytical and Physical Chemistry Section, Smith Kline & French Laboratories. Uv spectra were determined in EtOH, ir spectra were measured as Nujol mulls, unless otherwise specified, nmr spectra were measured in $CDCl_3$, and chemical shifts are reported in ppm downfield from TMS.

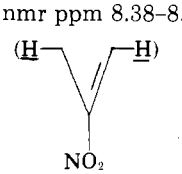
3,4-Dimethoxyphenylacetone. A mixture of 309 grams (1.55 moles) of 3,4-dimethoxyphenylacetic acid, 309 grams of anhydrous sodium acetate, and 1 liter of acetic anhydride was stirred under reflux for 18 hr. The viscous mass was cooled to 85° C, diluted with 1250 ml of water, and then with 1750 ml of 40% sodium hydroxide (gas evolved). The mixture was stirred on a steam bath for 4 hr, cooled, diluted with water, and extracted with chloroform five times. The chloroform phases were washed with water, dried, and concentrated. The residue was distilled in vacuo to give 150 grams (50%) of oil, bp 116–122° C at 1 mm [lit. (*33*), bp 142° C at 2.6 mm].

2-(3,4-Dimethoxyphenyl)-4-nitrophenol (3). λ_{max} μ 2.92 (OH), 6.63 and 7.51 (NO_2); nmr ppm 8.38–8.02 multiplet [2]



6.21–5.98 multiplet [4] (other aromatic protons); 2.94 singlet [6] (2 × OCH_3).

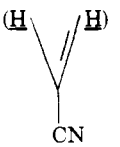
2-(3,4-Dimethoxyphenyl)-4-nitrophenol Benzyl Ether (4b). λ_{max} μ 6.62 and 7.44 (NO_2); 13.65 and 14.44 (monosubstituted benzene); nmr ppm 8.38–8.11 multiplet [2]



7.40 singlet [5] ($C_6H_5CH_2$); 7.27–7.01 multiplet [4] (other aromatic protons); 5.25 singlet [2] ($OCH_2C_6H_5$); 3.96 and 3.78 singlets [6] (2 × OCH_3).

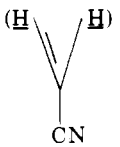
4-Benzyloxy-3-(3,4-dimethoxyphenyl)aniline (5b). λ_{max} μ 2.90 (NH_2); nmr ppm, 7.30 singlet [5] ($C_6H_5CH_2$); 7.3–6.5 multiplet [6] (other aromatic protons); 4.9 singlet [2] (OCH_2); 3.88 and 3.75 singlets [6] (2 × OCH_3); 3.36 singlet [2] (NH_2).

3-(3,4-Dimethoxyphenyl)-4-methoxybenzonitrile (7a). The crude reaction product was extracted repeatedly with benzene; the benzene was washed in turn with water, 5% sodium carbonate, and water. After being dried, the benzene was concentrated to a small volume and placed on a column of Woelm neutral alumina (activity –3). The column was washed further with benzene, and the desired nitrile weighing 4 grams was collected in the first 300 ml of eluate. λ_{max} μ 4.51 (CN); nmr ppm 8.05–7.82 multiplet [2]



7.43–7.22 multiplet [4] (other aromatic protons); 4.1 singlet [6] (2 × OCH_3); 4.05 singlet [3] (OCH_3).

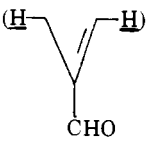
4-Benzyloxy-3-(3,4-dimethoxyphenyl)benzonitrile (7b). λ_{max} μ 4.53 (CN); nmr ppm 8.12–7.78 multiplet [2]



7.67 singlet [5] ($C_6H_5CH_2$); 7.49–7.25 multiplet [4] (other aromatic protons); 5.37 singlet [2] ($OCH_2C_6H_5$); 4.07 and 3.91 singlets [6] (2 × OCH_3).

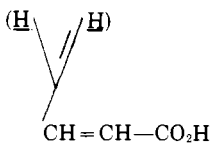
Washing the column with benzene after the elution of 7b gave two additional fractions of 500 ml (red) which were combined and evaporated. The residual red solid was recrystallized from dry ethanol (charcoal); it melted at 90–92° C and weighed 0.5 gram λ_{max} μ 4.53 (CN); λ_{max} mμ 252 (ϵ_{max} 28,900); 284 (sh ϵ_{max} 1805). Nmr ppm 7.82–7.01 multiplet [21] (aromatic protons); 5.42–5.17 (broad singlet) [4] (2 × OCH_2); 4.05 and 3.90 singlets [12] (4 × OCH_3).

3-(3,4-Dimethoxyphenyl)-4-methoxybenzaldehyde (8a). λ_{max} μ 3.71 (CHO) 5.91 (HC=O); nmr ppm 7.97–7.78 multiplet [2]



7.20–6.94 multiplet [4] (other aromatic protons); 3.94 singlet [9] (3 × OCH_3).

3-(3,4-Dimethoxyphenyl)-4-methoxycinnamic Acid (6a). λ_{max} μ 5.95 (CH=CH—COOH); nmr ppm 7.80 doublet [1], J = 16.5 Hz (>—CH=CH); 7.63–7.44 multiplet [2]



7.14–6.95 [4] (other aromatic protons); 6.4 doublet [1] (CH=CH—CO_2H); 3.94 singlet [6] (2 × OCH_3); 3.87 singlet [3] (OCH_3).

3-[3-(3,4-Dimethoxyphenyl)-4-methoxyphenyl]propionic Acid (9a). λ_{max} μ 5.88 (CH_2CH_2COOH); nmr ppm 7.27–6.98 multiplet [6] (aromatic protons); 3.92 singlet [6] (2 × OCH_3); 3.80 singlet [3] (OCH_3); 3.05–2.68 multiplet [4] ($ArCH_2$-CH_2COOH).

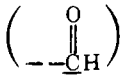
3-[3-(3,4-Dimethoxyphenyl)-4-methoxyphenyl]propionic Acid Methyl Ester (9a). λ_{max} μ 5.78 (CH_2CH_2COOMe); nmr ppm 7.17–6.90 multiplet [6] (aromatic protons); 3.94 singlet [6]

(2 × OCH_3); 3.81 singlet [3] (OCH_3); 3.71 singlet [3] ($CH_2CH_2CO_2CH_3$); 3.02–2.56 multiplet [4] ($ArCH_2CH_2CO_2Me$).

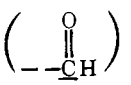
3 - [3 - (2-Chloromethyl-4,5-dimethoxyphenyl)-4-methoxyphenyl]propionic Acid (10a). λ_{max} μ 5.88 ($CH_2CH_2\underline{C}OOH$); nmr ppm 7.15–6.65 multiplet [5] (aromatic protons); 4.38 singlet [2] (CH_2Cl); 3.92, 3.83, and 3.72 singlets [9] (3 × OCH_3); 3.0–2.5 multiplet [4] (CH_2CH_2COOH).

3 - [3 - (2-Chloromethyl-4,5-dimethoxyphenyl)-4-methoxyphenyl]propionic Acid Methyl Ester (10b). λ_{max} ($CHCl_3$) μ 5.79 ($CH_2CH_2\underline{C}OOMe$); nmr ppm 7.27–6.63 multiplet [5] (aromatic protons); 4.41 singlet [2] (CH_2Cl); 3.96, 3.87, and 3.76 singlets [9] (3 × OCH_3); 3.68 singlet [3] ($CH_2CH_2COOCH_3$); 3.0–2.5 multiplet [4] ($CH_2CH_2COOCH_3$).

3 - [3 - (2-Formyl-4,5-dimethoxyphenyl)-4-methoxyphenyl]propionic Acid (1a). A mixture of 0.69 gram (4.6 mmol) of phosphorus oxychloride and 0.61 gram of *N*-methylformanilide was left at room temperature for 45 min. Then 1.5 grams (4.5 mmol) of 9b was added, and the mixture was stirred at 70° C for 5 hr under nitrogen. After standing at room temperature overnight under nitrogen, the thick, dark liquid was warmed and stirred into ice water. The aqueous mixture was extracted with ethyl acetate, and the ethyl acetate was washed with water and 5% sodium bicarbonate. The ethyl acetate was dried and evaporated. The residual oil weighed 1.5 grams and was chromatographed on a Woelm neutral alumina column (activity –3). The column was washed with a mixture of cyclohexane–ethyl acetate (90:10). Fractions of 25 ml were collected and monitored by TLC. Fractions 7–9 were combined (2,4-dinitrophenylhydrazine-positive) λ_{max} (natural film) μ 3.55 ($\underline{C}HO$); 5.77 ($CH_2CH_2\underline{C}OOCH_3$); 5.97



Fractions 7–9, after concentration, were treated with 5 ml of ethanol and 5 ml of 5% sodium hydroxide, and the mixture was stirred at room temperature for 90 min. The solution was acidified with dilute hydrochloric acid and extracted with ethyl acetate. The organic layers were washed with 5% sodium carbonate and water, and the combined aqueous phases were acidified and re-extracted into ethyl acetate. The ethyl acetate was dried and distilled. The gum remaining was triturated with ether, and a solid formed. λ_{max} μ 3.63 ($\underline{C}HO$); 5.82 ($CH_2CH_2\underline{C}OOH$); 6.12



($CHCl_3$) 3.56 ($\underline{C}HO$); 5.87 ($CH_2CH_2\underline{C}OOH$); 5.99 ($H\underline{C}O$); nmr ppm 9.48 singlet [1] (CHO); 7.42–6.72 multiplet [5] (aromatic protons); 3.80 singlet [6] (2 × OCH_3); 3.59 singlet [3] (OCH_3); 2.73–2.63 degenerate quartet [4], J = 6 Hz (CH_2CH_2COOH).

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