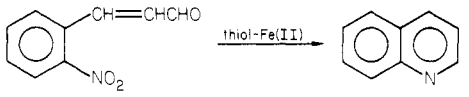
Table V. Preparation of Quinoline from o-Nitrocinnamaldehyde by Thiols-Fe(II)[a]

thiol (mM)	Fe^{2+}, mM	time, h	quinoline,[b] %
DHLAm (200)	1	15	15
	50	15	29
cysteine (400)	1	6	76[c]

[a] Conditions: [o-nitrocinnamaldehyde] = 50 mM, 50 °C, 0.2 M carbonate buffer (pH 9.8)-EtOH (1:3). [b] Isolated by Kugelrohr distillation. [c] Buffer-EtOH (1:1).

or cysteine in the presence of a catalytic amount of ferrous ion (eq 4, Table V). DHLAm-Fe(II) gave quinoline in



(4)

thiol, DHLAm; cysteine

poor yield (15%) presumably due to addition of DHLAm to the C=C bond, whereas cysteine iron(II) gave quinoline in good yield (76%) even in the aqueous solvent (buffer-EtOH).

Selective reduction of nitrobenzenes by iron/HCl[7] or Fe^{2+}/NH_4OH[8] require severe conditions of temperature and pH. Reduction by $Fe_3(CO)_{12}$-MeOH[9] or phthalocyaninecobalt(I) anion[10] give good results in mild conditions, but the former complex is somewhat hazardous and the latter one has less reactivity and is not so simple to handle. Reduction of substituted nitrobenzenes by the present thiol-Fe(II) system under weakly alkaline conditions was found to be a simple and selective method.

Experimental Section

General Procedure and Materials. GLC analyses were carried out on a JEOL JGC-1100 gas chromatograph (10% SE-30, stainless steel column, N_2 carrier gas).

Dihydrolipoamide (DHLAm) was prepared as reported[2] earlier. Other chemicals used in this study were reagent grade; solvents were purified by the usual procedure.

Reduction of Monosubstituted Nitrobenzenes. Monosubstituted nitrobenzenes (0.25 mmol) and DHLAm (207 mg, 1 mmol) were put into a Schlenk tube which was degassed and replaced with argon gas. To the Schlenk tube were added ethanol (3.75 mL), 0.2 M Menzel carbonate buffer (Na_2CO_3-$NaHCO_3$, pH 9.8) (1.0 mL), and a 20 mM ferrous ammonium sulfate aqueous solution (0.25 mL), which were previously bubbled with argon, and the reaction mixture was allowed to stir in a water bath at 50 °C for 15 h under argon. After the reaction, ethanol was removed by evaporation and the aqueous residue was extracted with ether. The organic layer was dried with anhydrous magnesium sulfate and evaporated to give a mixture of LAm, DHLAm, starting material, and product. Monosubstituted anilines were separated by column chromatography on silica gel (benzene:ether = 4:1). The trifluoroacetanilides of unstable anilines were formed as described previously[2] and isolated by the same method as above. Anilines and trifluoroacetanilides obtained were identified by melting or boiling points and IR and NMR spectra of authentic samples: p-aminobenzonitrile, mp 84-85 °C (lit.[11] mp 85 °C); p-aminoacetophenone, mp 104-106 °C (lit.[12] mp 106 °C); methyl p-aminobenzoate, mp 100-102 °C (lit.[13] mp 112 °C); trifluoroacetamide, mp 86-87 °C (lit.[14] mp 88.5-90 °C); N,N'-bis(trifluoroacetyl)-p-phenylenediamine, mp 240-250 °C (lit.[14] mp 251 °C); p-methyltrifluoroacetanilide, mp 121-123 °C (lit.[15] mp 123-124.5 °C); p-methoxytrifluoroacetanilide, mp 110-112 °C (lit.[15] mp 111-112 °C); p-chlorotrifluoroacetanilide, mp 121-123 °C (lit.[15] mp 123-124.5 °C); o-aminobenzaldehyde, mp 35-36 °C (lit.[8] mp 38-39 °C); o-phenylenediamine, mp 99-100 °C (lit.[16] mp 99-101 °C); anthranilamide, mp 109-110 °C (lit.[6] mp 110.5-111.5 °C); quinoline; bp_5 90-100 °C (Kugelrohr) (lit.[17] bp_{14} 110-114 °C). IR and NMR spectra[18] of o-aminoacetophenone and o-anisidine coincided completely with those of authentic samples.

Reduction of p-Nitroanisole by Thiols-Fe(II). The reduction was carried out by the same method described above using thiols instead of DHLAm. After the reaction, the reaction mixture was extracted with ether, and the organic layer was dried with magnesium sulfate and evaporated. The residue was dissolved in 5 mL of chloroform. The yield of p-anisidine was determined by GLC analysis of the chloroform solution with n-decane as an internal standard.

Registry No. DHLAm, 3884-47-7; NC-p-$C_6H_4NO_2$, 619-72-7; $CH_3C(O)$-p-$C_6H_4NO_2$, 100-19-6; MeOC(O)-p-$C_6H_4NO_2$, 619-50-1; Cl-p-$C_6H_4NO_2$, 100-00-5; $PhNO_2$, 98-95-3; Me-p-$C_6H_4NO_2$, 99-99-0; MeO-p-$C_6H_4NO_2$, 100-17-4; NH_2-p-$C_6H_4NO_2$, 100-01-6; NH_2-p-C_6H_4CN, 873-74-5; NH_2-p-$C_6H_4C(O)CH_3$, 99-92-3; NH_2-p-$C_6H_4C(O)OMe$, 619-45-4; Cl-p-$C_6H_4NH_2$, 106-47-8; $PhNH_2$, 62-53-3; Me-p-$C_6H_4NH_2$, 106-49-0; MeO-p-$C_6H_4NH_2$, 104-94-9; NH_2-p-$C_6H_4NH_2$, 106-50-3; $HS(CH_2)_2O(CH_2)_2SH$, 2150-02-9; PhSH, 108-98-5; $HS(CH_2)_2NH_2$, 60-23-1; $HS(CH_2)_2CO_2Na$, 42267-40-3; NO_2-o-$C_6H_4C(O)CH_3$, 614-21-1; NO_2-o-C_6H_4CHO, 552-89-6; MeO-o-$C_6H_4NO_2$, 91-23-6; NO_2-o-$C_6H_4NH_2$, 88-74-4; NO_2-o-C_6H_4CN, 612-24-8; NH_2-o-$C_6H_4C(O)CH_3$, 551-93-9; NH_2-o-C_6H_4CHO, 529-23-7; NH_2-o-C_6H_4OMe, 90-04-0; NH_2-o-$C_6H_4NH_2$, 95-54-5; ferrous ammonium sulfate, 10045-89-3; cysteine, 52-90-4; anthranilamide, 88-68-6; o-nitrocinnamaldehyde, 1466-88-2; quinoline, 91-22-5.

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Action of Diazomethane on (Z/E)-2-Methyl(or phenyl)-4-benzylidene-5(4H)-oxazolones

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Received August 4, 1983

We have been interested in the synthesis of (Z/E)-2-methyl(or phenyl)-4-(α-arylethylidene)-5(4H)-oxazolones **5** and **6** for several years. Although earlier authors[1] found that acetophenones and hippuric acid could not condense under Plöchl-Erlenmeyer conditions, 2-phenyl derivatives were prepared[2] with moderate or low yields in acetic anhydride and lead acetate as isomeric mixtures with the Z isomer predominating. The pure isomers were obtained by crystallization or by suitable isomerization procedures. Attempts to prepare 2-methyl derivatives have been unsuccessful. On the other hand several workers[3] have in-

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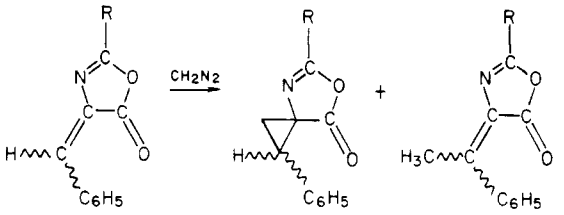
Table I. Comparative Yields (%) in THF for the Reaction of Diazomethane with 1 and 2



1, R = C_6H_5 3, R = C_6H_5 5, R = C_6H_5
2, R = CH_3 4, R = CH_3 6, R = CH_3

	yield of				total
	3Z	3E	5Z	5E	yield
1Z	33(31)[a]	9	48	0	90
1E	18	55(54)[a]	0	17	90

	yield of				total
	4Z	4E	6Z	6E	yield
2Z	9	4	42	0	55

[a] Underlined values have been previously reported (ref 4), using methylene chloride as solvent.

Table II. Comparative Yields (%) for the Reaction of Diazomethane with 1Z in Different Solvents

	3Z	3E	5Z
CCl_4	55	15	20
THF	33	9	48
DMF	28	8	54

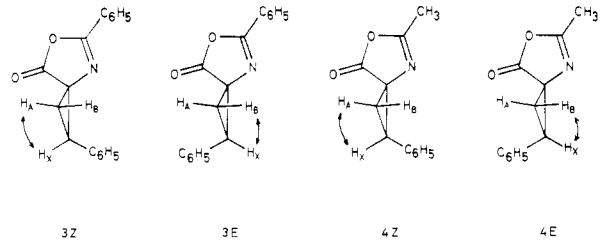
vestigated the cyclopropanation of 2-phenyl-4-arylidene-5(4*H*)-oxazolones with diazomethane and recently[4] both *Z* and *E* cyclopropylogues of DL-phenylalanine have been prepared by the cyclopropanation of each 2-phenyl-4-benzylidene-5(4*H*)-oxazolone isomer with diazomethane to form the three-membered ring in moderate yields.

We now report on the reaction of (*Z*/*E*)-2-methyl(or phenyl)-4-benzylidene-5(4*H*)-oxazolones **1** and **2** with diazomethane. **1Z** and **2Z** were easily obtained by standard procedures[5] from benzaldehyde and the corresponding aceturic or hippuric acid, and **1E** was prepared by isomerization of **1Z** with hydrobromic acid.

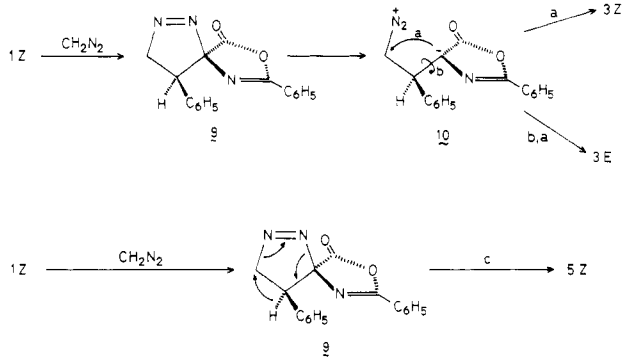
The addition of diazomethane to double bonds activated by a suitable electron-withdrawing group, followed by thermal decomposition of the resulting pyrazolines, is an established route to cyclopropanes,[6] although the synthetic utility of the method is hampered by extensive formation of unsaturated compounds. Von Auwers and König studied the stereochemistry of the preparation of cyclopropanes by this method and concluded that the cyclopropanes formed retain the geometry of the initial olefins.[7]

In our case the action of gaseous diazomethane[8] on (*Z*/*E*)-2-methyl(or phenyl)-4-benzylidene-5(4*H*)-oxazolones

Scheme I



Scheme II



gave a three-compound mixture, two stereoisomeric spiroazalactones and the (*Z*/*E*)-2-methyl(or phenyl)-4-(α-phenylethylidene)-5(4*H*)-oxazolone, which retained the initial oxazolinone geometry. The ratio 5(4*H*)-oxazolone/spiroazalactones depended on the solvent polarity and the initial oxazolinone structure[9] (Tables I and II). That is to say, in contrast to the results of von Auwers and König[7] and in accordance with Van Auken and Rinehart,[10] the cyclopropanation proceeds with loss of geometry, although there is a slight degree of stereoselectivity. the extensive formation of the unsaturated compounds **5** and **6** with retention of the geometry is remarkable.

Structural assignments for all products have been made on the basis of the ^1H NMR spectral data (Table III). The signals due to the protons on the cyclopropyl ring appear as doublets of doublets. the lower field signals are assigned to the benzylic proton, H_X. The geminal protons, H_A and H_B, vicinal to H_X could be assigned by comparisons of their vicinal coupling constants since it has been found that for vicinal cyclopropyl ring protons J_{cis} is generally larger than J_{trans}[11] (Scheme I). However, it was not possible to assign the signals unambiguously in **3Z** and **3E** or **4Z** and **4E** because of the small differences in their coupling constants. It is possible to make an unambiguous assignment of the ring protons by comparison of their chemical shifts with those previously reported[4] (with NOE experiment) for **3Z** and **3E**. Structural assignments for **5Z** and **5E** were made, as previously described,[2] on the basis of the ^1H NMR spectral data (Table III): the methyl group of **5Z** gave rise to a low-field signal as it is cisoid with respect to the carbonyl group.

The mechanism of the addition of diazomethane to the double bond to afford cyclopropanes and unsaturated compounds is uncertain, although it has been suggested that pyrazolines are probable intermediates[3a] on the basis of the isolation of such compounds when diazomethane

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(8) We use gaseous diazomethane to study the solvent influence on the product ratios without changes on the solvent polarity, but for synthetic purpouses we advise the use of ethereal solution of diazomethane.

(9) In order to obtain comparative yields, the three compounds were separated chromatographically over silica, eluting with benzene.

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Table III. ^{1}H NMR Spectral Data for 3-6[a]

compd	chemical shift, δ							coupling constants, Hz		
	CH_3	R = CH_3	R = C_6H_5	C_6H_5	H_X	H_A	H_B	J_{AB}	J_{AX}	J_{BX}
3Z			7.2-7.5 (m, 3 H), 7.8-8.0 (m, 2 H)	7.31 (s, 5 H)	3.18 (dd)	2.22 (dd)	2.32 (dd)	-5.3	10.0	8.6
3E			7.2-7.6 (m, 3 H), 7.8-8.0 (m, 2 H)	7.26 (s, 5 H)	3.46 (dd)	2.30 (d)	2.30 (d)	0	9.3	9.3
4Z		2.21 (s, 3 H)		7.29 (s, 5 H)	3.09 (dd)	2.11 (dd)	2.23 (dd)	-5.3	10.0	8.6
4E		2.24 (s, 3 H)		7.29 (s, 5 H)	3.34 (dd)	2.20 (d)	2.20 (d)	0	9.3	9.3
5Z	2.75 (s, 3 H)		7.4-7.6 (m, 6 H),	7.8-8.2 (m, 4 H)						
5E	2.56 (s, 3 H)		7.3-7.6 (m, 8 H),	8.0-8.2 (m, 2 H)						
6Z	2.70 (s, 3 H)	2.30 (s, 3 H)		7.4-7.6 (m, 3 H), 7.7-7.9 (m, 2 H)						

[a] All compounds were dissolved in $CDCl_3$ with Me_4Si as the internal standard.

reacts with other ethylene derivatives.

The mechanism of decomposition of 1-pyrazolines has been recently reviewed.[12] Cyclopropane formation is in accordance with the ionic mechanism of the decomposition of 1-pyrazolines, proposed in Van Auken's work[10] and later by others.[13] The stereospecifity of the cleavage of 1-pyrazoline **9** is lacking, although stereoselectivity does exist as cyclization a to **3Z** would be favored over rotation b and cyclization a to **3E** in the intermediate **10** (Scheme II).

Several mechanisms have been proposed to explain stereospecific formation of unsaturated compounds from related 1-pyrazolines.[13-15] Hydride shift in the 1-pyrazoline intermediate **9** with loss of nitrogen would give **5Z** (Scheme IIc).

In conclusion the experimental conditions used by Stammer and co-workers are suitable for the synthesis of spiroazalactones although in apolar solvents better yields can be obtained. On the other hand unsatured 5(4*H*)-oxazolones can be preferably obtained in aprotic polar solvents.[16] This procedure constitutes an interesting and improved alternative to the synthesis of (*Z*)-2-phenyl-4-(α-arylethylidene)-5(4*H*)-oxazolones and it is the only procedure to the synthesis of (*Z*)-2-methyl-4-(α-arylethylidene)-5(4*H*)-oxazolones. *E* isomers can be obtained with very poor yield, so we advise their synthesis from the corresponding *Z* isomers by isomerization with hydrobromic acid as we have previously reported.[2]

Experimental Section

All melting points were taken on a Büchi 510 capillary melting point apparatus and are uncorrected. Infrared spectra were measured with a Perkin-Elmer Model 283 recording spectrophotometer, reported values are given in cm^{-1}. ^{1}H NMR spectra were recorded at 90 MHz with a Perkin-Elmer Model R-32 spectrometer in $CDCl_3$ with Me_4Si as internal standard. Microanalyses were measured on a Perkin-Elmer Model 240-B analyzer.

(*Z*)-2-Phenyl-4-benzylidene-5(4*H*)-oxazolone (1Z) and (*Z*)-2-methyl-4-benzylidene-5(4*H*)-oxazolone (2Z) were prepared by the general procedure employed by Rao,[5] by condensing the benzaldehyde with hippuric or aceturic acid in the presence of acetic anhydride and sodium acetate to yield 80% of **1Z** and 75% of **2Z**. (*E*)-2-Phenyl-4-benzylidene-5(4*H*)-oxazolone (**1E**) was prepared by the general method employed by Rao.[5] Isomerization of **1Z** in saturated hydrobromic acid gave 100% of **1E**.

Preparation of Gaseous Diazomethane. CAUTION! Diazomethane is a very harmful and hazardous reagent and must be handled with caution.[17] The preparation of a great amount of diazomethane must be avoided, and the reagent must be bubbled through the reaction solution directly to consume it immediately.

A total of 3 mL of 40% potassium hydroxide solution and 10 mL of carbon tetrachloride are placed in a 50-mL two-necked flask and cooled at -5 °C; then 1 g of *N*-methyl-*N*-nitrosourea is added in small quantities with magnetic stirring. After the addition of the *N*-methyl-*N*-nitrosourea the solution is lightly heated at 50 °C, and the diazomethane is distilled under atmosphere of nitrogen and directly bubled through the reaction solution until the carbon tetrachloride is colorless.

Action of Diazomethane with (*Z*)-2-Phenyl-4-benzylidene-5(4*H*)-oxazolone (1Z). Gaseous diazomethane (from *N*-methyl-*N*-nitrosourea in carbon tetrachloride) was bubbled through a solution of 1 g of **1Z** in 10 mL of tetrahydrofuran[18] freshly distilled until no **1Z** was noticed by thin-layer chromatography. The solution was concentrated in vacuo and the resultant yelow oil dried. The whole yellow solid was dissolved in the minimum amount of warm benzene, and the three compounds of the mixture were separated by column chromatography (SiO_2, 70–280 mesh) using benzene as eluting agent to afford analitically pure samples of the three compounds in this order: first 500 mg (48%) of (*Z*)-2-phenyl-4-(α-phenylethylidene)-5-(4*H*)-oxazolone (**5Z** mp 101–103 °C (lit.[2] mp 104 °C), IR (Nujol) 1780 (C=O); later 350 mg (33%) of (*Z*)-1,5-diphenyl-6-oxa-4-azaspiro[2.4]hept-4-en-7-one (**3Z**), mp 141–142 °C (lit.[4] mp 142–143 °C), IR (Nujol) 1805 (C=O); and finally 95 mg (9%) of (*E*)-1,5-diphenyl-6-oxa-4-azaspiro[2.4]hept-4-en-7-one (**3E**), mp 110–112 °C (lit.[4] mp 115–117 °C), IR (Nujol) 1810 (C=O).

Action of Diazomethane with (*E*)-2-Phenyl-4-benzylidene-5(4*H*)-oxazolone (1E). Gaseous diazomethane (from *N*-methyl-*N*-nitrosourea in carbon tetrachloride) was bubbled through a solution of 1 g of **1E** in 10 mL of tetrahydrofuran freshly distilled until no **1E** was noticed by thin-layer chromatography. The solution was concentrated in vacuo and the resultant yellow oil dried. The whole yellow solid was dissolved in the minimum amount of warm benzene, and the three compounds of the mixture were separated by column chromatography (SiO_2, 70–230 mesh) using benzene as eluting agent to afford analitically pure samples of the three compounds in this order: first 180 mg (17%) of (*E*)-2-phenyl-4-(α-phenylethylidene)-5-(4*H*)-oxazolone (**5E**), mp 108–110 °C (lit.[2] mp 110 °C), IR (Nujol) 1775 (C=O); later 190 mg (18%) of (*Z*)-1,5-diphenyl-6-oxa-4-azaspiro[2.4]hept-4-en-7-one (**3Z**), mp 141–142 °C (lit.[4] mp 142–143 °C), IR (Nujol) 1805 (C=O); and finally 580 mg (55%) of (*E*)-1,5-diphenyl-6-oxa-4-azaspiro[2.4]hept-4-en-7-one (**3E**), mp 110–112 °C (lit.[4] mp 115–117 °C), IR (Nujol) 1810 (C=O).

Action of Diazomethane with (*Z*)-2-Methyl-4-benzylidene-5(4*H*)-oxazolone (2Z). Gaseous diazomethane (from *N*-methyl-*N*-nitrosourea in carbon tetrachloride) was bubbled through a solution of 1 g of **2Z** in 10 mL of tetra-

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(15) (a) Hamelin, J.; Carrié, R. *Bull. Soc. Chim. Fr.* **1968**, 2521. (b) Hamelin, J.; Carrié, R. *Ibid.* **1972**, 2054.
(16) In protic polar solvents the action of diazomethane on 5(4)-oxazolones gave an opened oxazolinone ring.
(17) Vogel, A. "Vogel's Textbook of Practical Organic Chemistry"; Longman Inc: New York, 1978; p 289, 291.
(18) For yields in other solvents, see Table II.

hydrofuran freshly distilled until no **2Z** was noticed by thin-layer chromatography. The solution was concentrated in vacuo and the resultant yellow oil dried. The whole yellow solid was dissolved in the minimum amount of warm benzene, and the three compounds of the mixture were separated by column chromatography (SiO_2, 70–230 mesh) using benzene as eluting agent to afford analitically pure samples of the three compounds in this order: first 450 mg (42%) of (*Z*)-2-methyl-4-(α-phenylethylidene)-5-(4*H*)-oxazolone (**6Z**), mp 116–117 °C, IR (Nujol) 1770 (C=O) [Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.64; H, 5.47; N, 6.97. Found: C, 71.73; H, 5.36; N, 6.95,]; later 95 mg (9%) of (*Z*)-1-phenyl-5-methyl-6-oxa-4-azaspiro[2.4]hept-4-en-7-one (**4Z**), mp 193–194 °C, IR (Nujol) 1810 (C=O) [Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.64; H, 5.47; N, 6.97. Found: C, 71.89; H, 5.62; N, 6.93,]; and finally 43 mg (4%) of (*E*)-1-phenyl-5-methyl-6-oxa-4-azaspiro[2.4]-hept-4-en-7-one (**4E**), mp 218–219 °C; IR (Nujol) 1800 (C=O) [Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.64; H, 5.47; N, 6.97. Found: C, 71.50; H, 5.38; N,7.09.].

Registry No. **1E**, 15732-43-1; **1Z**, 17606-70-1; **2Z**, 38879-46-8; **3E**, 64283-24-5; **3Z**, 64283-23-4; **4E**, 87378-64-1; **4Z**, 87378-66-3; **5E**, 57427-91-5; **5Z**, 69015-75-4; **6Z**, 87378-63-0; benzaldehyde, 100-52-7; aceturic acid, 543-24-8; hippuric acid, 495-69-2; diazomethane, 334-88-3.

Studies Aimed at the Synthesis of Morphine. 7.[1] Biomimetic Total Synthesis of (±)-Pallidine

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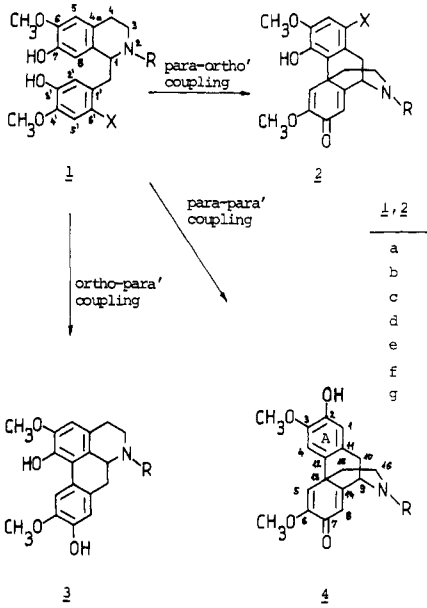
Received October 4, 1983

In plants morphinandienone-type alkaloids arise via phenolic oxidative coupling of 1-benzyl-1,2,3,4-tetrahydroisoquinolines. This transformation, which is considered to be the key step of the biogenesis of morphinans as well, has been suggested by Gulland and Robinson[2] and confirmed and refined by Barton and Cohen.[3] The first step of the reticuline (**1a**) → salutaridine (**2a**) → thebaine → morphine pathway requires a regioselective para–ortho′ oxidative coupling, which was in vitro detected (0.03% yield determined by an isotope dilution technique) first by Barton et al.[4] in 1963 and realized recently in preparative scale (2.7%) by our group[5] using lead tetraacetate in the presence of trichloroacetic acid. The great many attempts for the oxidation of reticuline (**1a**) using MnO_2,[6] $K_3Fe(CN)_6$,[4b,7] $AgCO_3$/Celite,[7d] and $VOCl_3$[7d,8] afforded mainly aporphinic isoboldine (**3a**) (ortho–para′ coupling) and isosalutaridine (**4a**) (para–para′) in 0.3–4% yield[9] (Scheme I). The dextrorotatory antipode of the latter has also been found as an alkaloid of *Corydalis pallida* var. *tenuis* (Yatabe) named pallidine.[13]

Scheme I



1,2	R	X
a	CH_3	H
b	$CO_2C_2H_5$	H
c	$CO_2C_2H_5$	Br
d	$CO_2C_2H_5$	Cl
e	CHO	H
f	CHO	Br
g	CHO	Cl

3,4	R
a	CH_3
b	$CO_2C_2H_5$
c	CHO

In the biomimetic approach of morphine the para–ortho′ coupling has been accomplished in remarkably higher yield, when instead of reticuline (**1a**), *N*-acylnorreticulines **1b–g** were used as starting materials. In these oxidative cyclizations thallium tris(trifluoroacetate),[14,15] lead tetraacetate, or different organic iodo compounds[1,16] proved to be effective in supplying *N*-acylnorsalutaridines **2b–g** regioselectively.

Now we report the successful utilization of manganese and vanadyl acetonylacetonate for the selective formation of *N*-acylnorisosalutaridines **4b,c** via para–para′ coupling of the corresponding *N*-acylnorreticulines.

Treatment of *N*-(ethoxycarbonyl)norreticuline (**1b**)[16,17,21] with 5 equiv of manganese tris(acetonylacetonate) in boiling absolute acetonitrile afforded *N*-(ethoxycarbonyl)norisosalutaridine (**4b**) in 32% yield[18] along with a small amount of *N*-(ethoxycarbonyl)norisoboldine (**3b**).

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0022-3263/84/1949-1439$01.50/0