HETEROCYCLES, Vol. 3, No. 11, 1975

APPLICATION OF LEAD TETRAACETATE OXIDATION TO THE SYNTHESIS OF ISOQUINOLINE ALKALOIDS

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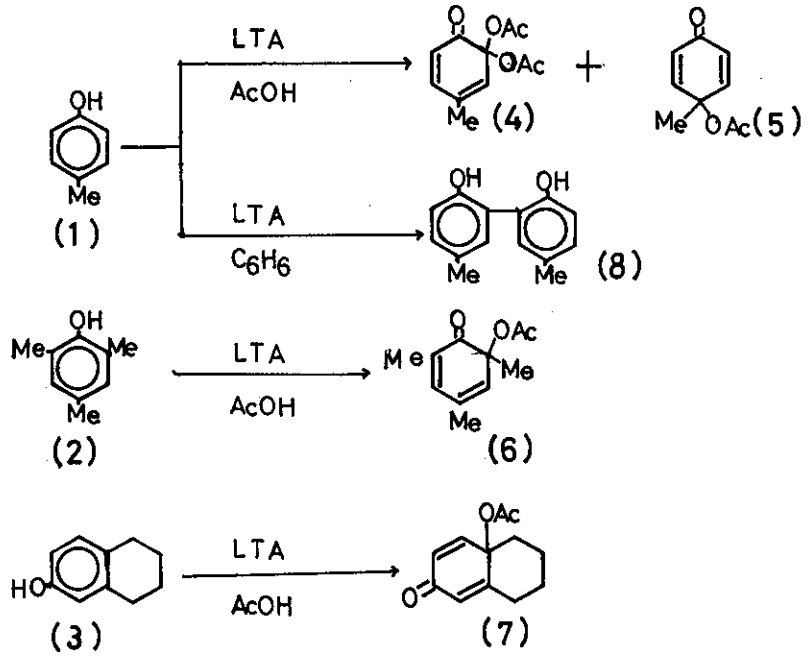
A variety of 7- or 6-tetrahydroisoquinolinols are readily oxidized with lead tetraacetate in acetic acid or methylene chloride to give p-quinol acetates or 4-acetates, whose acid treatment has produced (±)-aporphines, (±)-homoaporphines, (±)-homomorphinandienones, and (±)-homoproaporphines or (±)-isopavines, respectively.

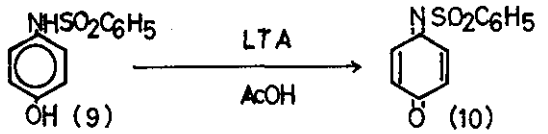
Introduction

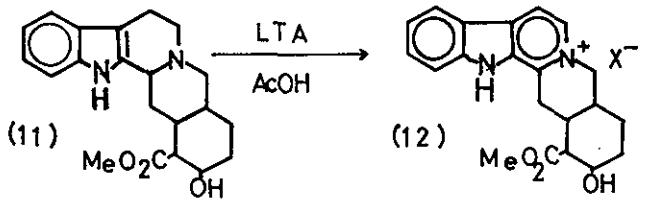
Lead tetraacetate (LTA) is one of the versatile oxidizing agents[1] in organic synthesis. In particular, its specific mode[2] of oxidation towards phenols is well documented by the pioneering work of Wessely[3], Hecker[4], and Witkop[5]. These authors indicate that, for example, p-cresol (1), 2,4,6-trimethylphenol (2), and 2-decalinol (3) are converted when

oxidized in acetic acid (AcOH) to o-quinone diacetate (4)[3] and p-quinol acetate (5)[3], o-quinol acetate (6)[6], and p-quinol acetate (7)[3-5], respectively.



On the other hand, (1) is known to give 2,2'-biphenyl (8)[6], when oxidized in benzene. Furthermore, reaction[7] of organic nitrogen compounds by LTA causes oxidation at the grouping containing nitrogen, typical examples being the formation of quinone monoimides [(9)→(10)][8] and the dehydrogenation of yohimbine [(11)→(12)][9].

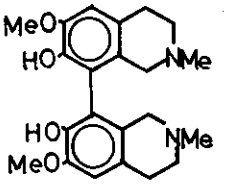




As part of a program[10] aimed at the synthesis of isoquinoline alkaloids[11] we planned to use the oxidant to oxidize phenolic tetrahydroisoquinolines expecting that the corresponding o- and p-quinol acetates would be formed and that they might undergo entirely different reactions from those of the former. The present review is concerned with LTA oxidation of some isoquinolinols and its application to the synthesis of isoquinoline alkaloids.

LTA Oxidation of 1,2,3,4-Tetrahydro-7-isoquinolinols

We started our study with the simplest model compound, corypalline (13a)[12]. Roughly speaking, three possible oxidation products were considered at the outset: namely i) bicorypalline (14)[10a,12], ii) o-quinone diacetate (15) and/or p-quinol acetate (16a), and iii) 3,4-dihydro-(17) and/or isoquinolinium salt (18).



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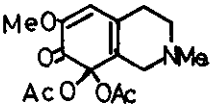

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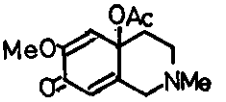
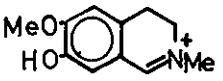


(16a)



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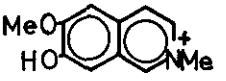
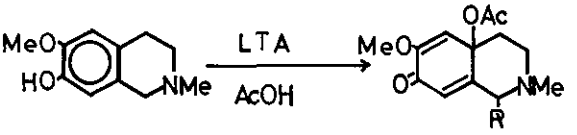


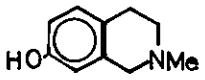
(18)

(13a) was oxidized with LTA in AcOH at room temperature to lead, after chromatography followed by recrystallization, to 10-acetoxy-$\Delta^{5,6,8,9}$-hexahydro-7-keto-6-methoxy-2-methylisoquinoline (p-quinol acetate)(16a)[13] in 20% yield, although the crude product formed in quantitative yield was not as impure as apparent by thin layer chromatography (TLC). Furthermore, similar oxidation in absolute ethanol (at room temperature) or absolute benzene (at reflux) gave (16a) in 13 or 15% yield, respectively, regardless of the solvent used.



(13) (16) a R = H 20%
b R = Me 18%
c R = C_6H_5 28%
d R = C_7H_7 14%

In the reaction, the presence of both an ortho-methoxyl and N-methyl group is a necessary requirement, because 7-hydroxy-tetrahydroisoquinoline (19) or 7-hydroxy-6-methoxytetraline (20) gave, when oxidized with LTA, none of the desired product.



(19)

(20)

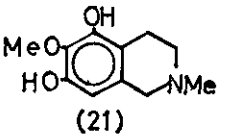
A similar reaction of 1-substituted 7-hydroxy-6-methoxy-tetrahydroisoquinolines (13b-d) took place to produce p-quinol acetates (16b-d)[13] in moderate yields.

Care must be taken to avoid overheating during removal of the solvent, since these p-quinol acetates are comparatively sensitive to heat.

Some Reactions of the p-Quinol Acetates

The p-quinol acetates (16) possess formally two characteristic groupings, one being the cross-conjugated dienone and the other the 3-acetoxy vinyl ether. Under certain acidic conditions, the former would undergo dienone-phenol type rearrangement[14] giving rise to phenols, such as (21), (22), and (23), which have an oxygenation pattern isomeric with the Cactus alkaloid, anhalidine (24)[15].

On the other hand, acid treatment of the latter would undergo an allylic type rearrangement[16].



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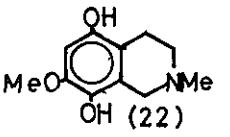

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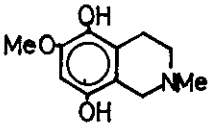

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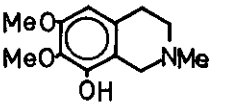
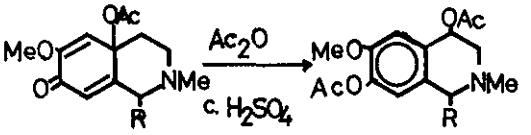


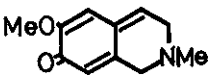
(24)

Quite unexpectedly, actual treatment with acetic anhydride (Ac_2O)-*conc. sulfuric acid* (H_2SO_4)*(Thiele's condition)*[14] *of* (16a) gave 4,7-diacetoxy-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (4,7-diacetate)(25a)[13] in 47% yield. Similarly, 4,7-diacetates (25b-d)[13] were formed in fair yields.



(16) (25)

a	R = H	47%
b	R = Me	16%
c	R = C_6H_5	34%
d	R = C_7H_7	43%

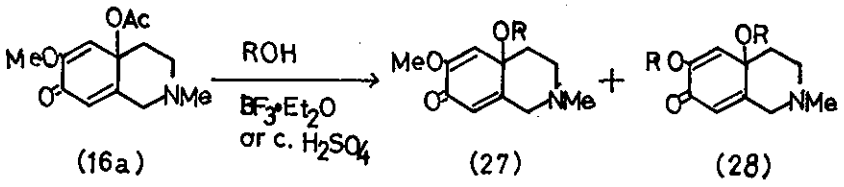


(26)

In addition, the 4-acetoxy group in (25a) could readily be replaced by a variety of nucleophiles (alcohols[17], thiols[17b,18a], amines[18], and some representative active methylene compounds[19]) under basic conditions. Mechanistically, an intermediate (26) with a quinone methide[20] structure is postulated for both of the above reactions.

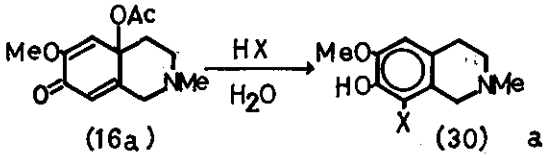
In contrast to the reaction with Ac_2O-conc. H_2SO_4, reaction

of (16a) with alcohols in the presence of boron trifluoride etherate (or conc. H_2SO_4) at room temperature yielded two kinds of quinol ethers [(27) and (28)][21] (R=CH_3, C_2H_5, n-C_3H_5 etc.). So far, this is the only one reaction, in which the 3-acetoxy vinyl ether system played a major role.



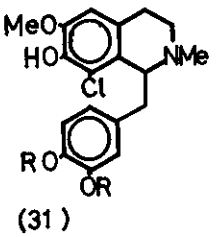
(16a) (27) (28)

Moreover, (16a) was smoothly transformed by use of aq. hydrochloric (HCl), aq. hydrobromic, and aq. hydroiodic acid to 8-chloro, 8-bromo-, and 8-iodo-corypalline (30a-c)[22], respectively.



(16a) (30) a X = Cl 78 %
b X = Br 75 %
c X = I 11 %

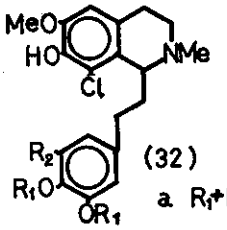
Likewise[22], 8-chloro-benzyl (31a,b) and -phenethyl (32a-c) tetrahydroisoquinolines were formed in fair to good yields.



(31)

a R+R=CH_2 71 %

b R=Me 43 %



(32)

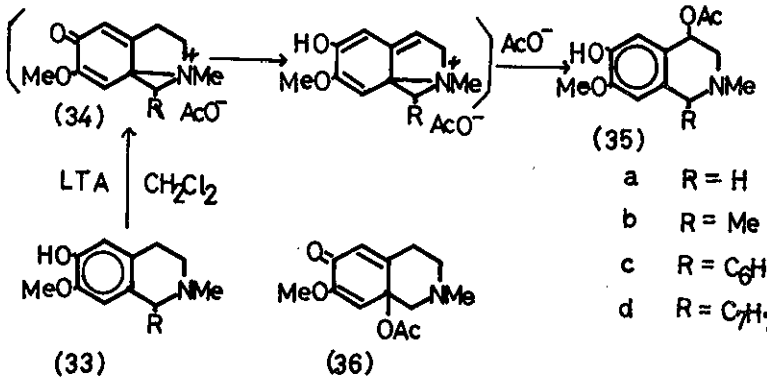
a R_1+R_1=CH_2, R_2=H 49%

b R_1=Me, R_2=H 44%

c R_1=Me, R_2=OMe 57%

LTA Oxidation of 1,2,3,4-Tetrahydro-6-isoquinolinols

In order to clarify the scope and limitation of the present reaction, LTA oxidation of corypalline (13a) isomers in which the methoxyl group is located at the ortho-position to the hydroxyl is of special interest. Therefore, at first, 6-hydroxy-7-methoxytetrahydroisoquinoline (33a) was oxidized with LTA in methylene chloride (CH_2Cl_2) or chloroform under ice-cooling to give, after purification on alumina, 4-acetoxy-1,2,3,4-tetrahydro-6-hydroxy-7-methoxy-2-methylisoquinoline (35a)[23] in 54% yield, instead of the corresponding p-quinol acetate (36).



(34) (33) (36)

(35)

a R = H 54 %

b R = Me 54%

c R = C_6H_5 48%

d R = C_7H_7 43%

Similarly, 1-substituted-6-hydroxy-7-methoxytetrahydroisoquinolines (33b-d) were converted to their corresponding 4-acetoxy derivatives (35b-d)[23] in moderate yields.

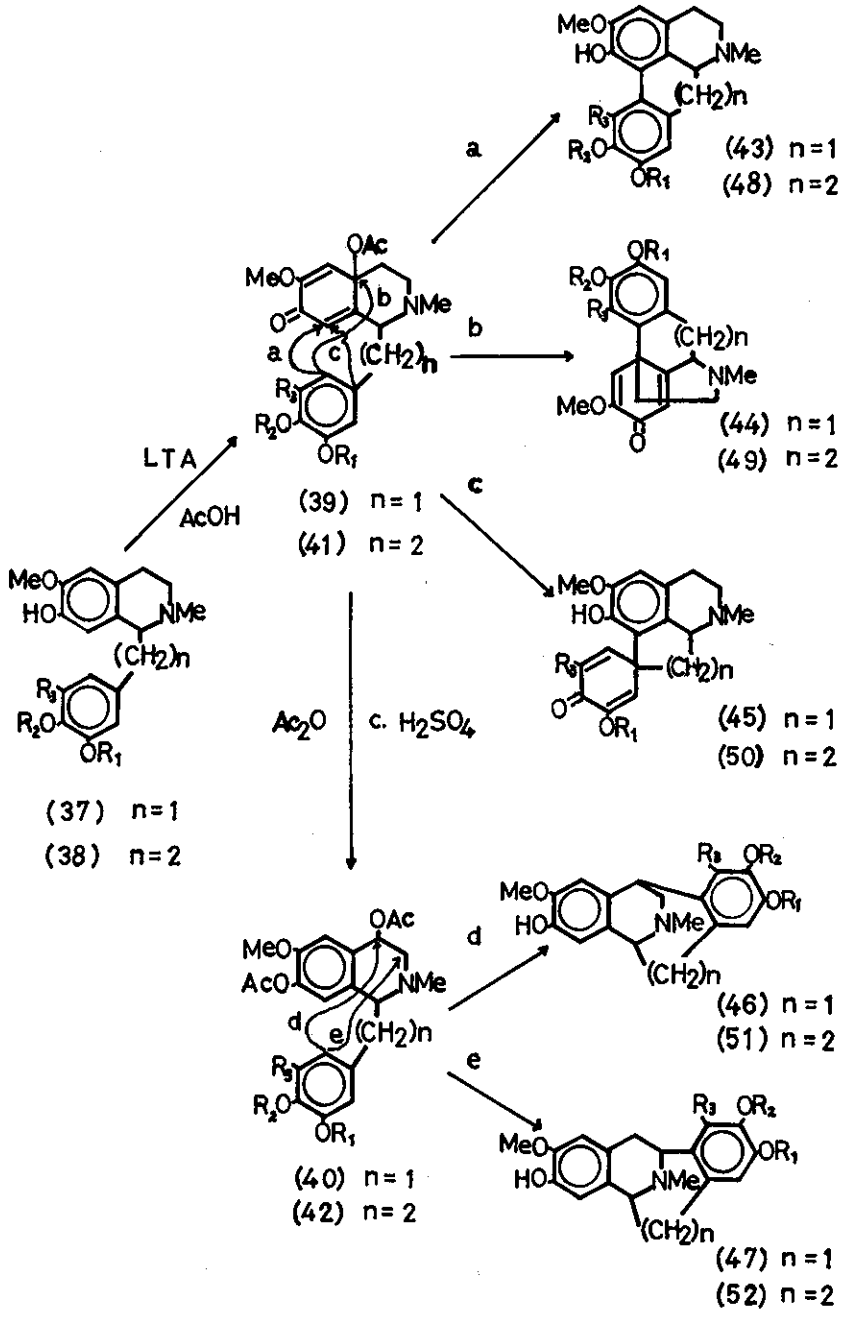
A mechanistic pathway leading to (35) can be visuallised as shown in the chart. Namely, preferential attack of nitrogen lone pair electrons at 9-position in the oxidation step results in the formation of an aziridinium dienone intermediate such as (34) enolization of which with concomitant aromatization in the presence of acetate ion (or acetic acid) results in the production of (35). The same intermediate as above has been proposed by Bobbitt[12] in the electro-oxidation of (33a).

Synthesis of Isoquinoline Alkaloids

Kametani and coworkers[24] have energetically performed the synthesis of a variety of isoquinoline alkaloids chiefly by means of basic chemical reactions such as phenolic oxidation[25], Pschorr[26] and benzyne[27] reactions, thermolysis[28], and photolysis[29].

Whereas Tobinaga's[30] and Miller's group[31] have accomplished the synthesis of morphinandienone alkaloids by electrochemical oxidation, Schwartz and coworkers[32] have synthesized O-methylandrocymbine[32a] and morphine alkaloids[32b] with the aid of thallium (III) trifluoroacetate (TTFA).

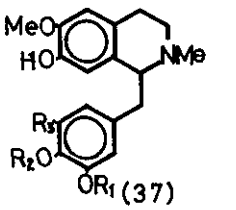
Now that p-quinol acetates (16) and 4,7-diacetates (25) were prepared in fair yields, our interest was naturally directed to the synthesis of several isoquinoline alkaloids by way of these intermediates. In principle, if we could obtain similar


MeO
HO
NMe
(CH2)n
R3
R2O
OR1
(43) n=1
(48) n=2
a
OAc
b
c
(39) n=1
(41) n=2
LTA
AcOH
(37) n=1
(38) n=2
b
(44) n=1
(49) n=2
c
(45) n=1
(50) n=2
Ac2O
c. H2SO4
AcO
d
e
(40) n=1
(42) n=2
(46) n=1
(51) n=2
(47) n=1
(52) n=2

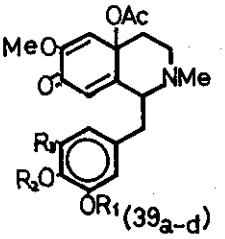
results with respect to properly activated 1-benzyl and 1-phenethyltetrahydroisoquinolines [(37) and (38)], acid treatment of the products [(39) or (40)] and [(41) or (42)] would afford aporphine (43), morphinandienone (44)[33], proaporphine (45), isopavine (46) or pavine (47) alkaloids[11] and their homologs (48-52)[11] as depicted in the scheme (reactive sites are shown by curved arrows).

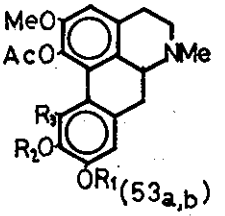
1. Aporphines

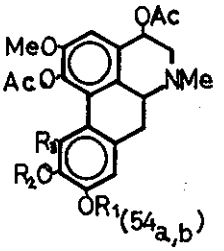
To activate the benzene ring, it was necessary to have an oxygen-function such as a methoxyl, methylenedioxy or benzyloxyl group in the para-position to the reacting site.



	R_1	R_2	R_3
a	Me	Me	H
b	CH_2		H
c	Me	C_7H_7	H
d	C_7H_7	Me	H





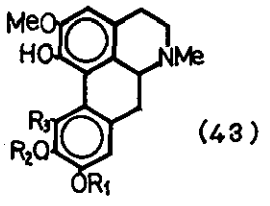


In practice, appropriate phenolic tetrahydroisoquinolines (37) were oxidized with LTA in AcOH at room temperature to give quantitatively the corresponding p-quinol acetates (39),

acid treatment of which was carried out without purification at room temperature.

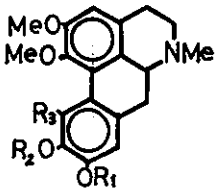
Thus, the p-quinol acetate (39a) of (±)-codamine (37a) was treated with conc. H_2SO_4 in Ac_2O to yield (±)-O-acetylthaliporphine (53a)[34] in 14% yield and a diastereomeric mixture of (±)-4-acetoxy-O-acetylthaliporphine (54a)[34] in 6% yield, which could be separated into two diastereomers. Hydrolysis of the former gave (±)-thaliporphine (43a)[34,35] in 68% yield. On similar treatment of the p-quinol acetate (39b) from (37b), (±)-O-acetyldomesticine (53b)[36] and diastereomeric (±)-4-acetoxy-O-acetyldomesticines (54b)[36] were formed in 18 and 10.2% (ca 1:1.2) yield, respectively. Basic hydrolysis of the former led to (±)-domesticine (43b)[27,36] in 83% yield. Methylation with diazomethane (CH_2N_2) of (43a) and (43b) gave (±)-glaucine (55a) and (±)-nantenine (-55b)[37], respectively.

Later, trifluoroacetic acid (TFA) in CH_2Cl_2 was proved to be much more effective for aporphine cyclization[38]. By this reagent, (43a) and (43b) were directly prepared in 96 and 84% yield, respectively. Likewise, aporphine (56)[38] was obtained in 48% yield.



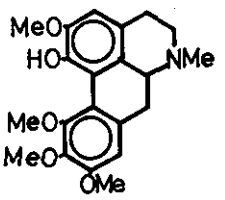
(43)

	R_1	R_2	R_3
a	Me	Me	H
b	CH_2		H
c	Me	C_7H_7	H
d	C_7H_7	Me	H
e	Me	H	H
f	H	Me	H



(55)

	R_1	R_2	R_3
a	Me	Me	H
b	CH_2		H
c	Me	H	H
d	H	Me	H



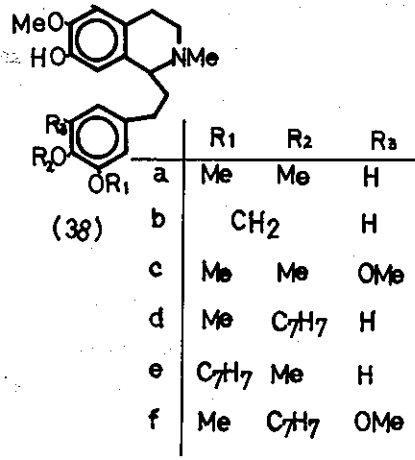
(56)

The phenolic 4'-benzyloxytetrahydroisoquinoline (37c) was transformed to its p-quinol acetate, which was treated with TFA in CH_2Cl_2 to give (±)-O-benzylbracteoline (43c)[39] in 48% yield. Hydrogenolysis with palladium (Pd) on carbon left (±)-bracteoline (43e)[40] in 60% yield. Likewise[39], (±)-O-benzyl-isoboldine (43d) and (±)-isoboldine (43f)[35d] were obtained in 44 and 88% yield, respectively. Methylation with CH_2N_2 followed by hydrogenolysis of (43c) and (43d) gave (±)-aporphine (55c)[39] and (±)-N-methyllaurotetanine (55d)[39,41] in yields of 88 and 52%.

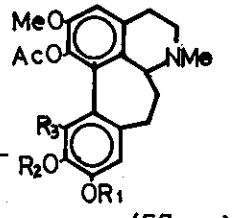
Up to the present, neither morphinandienones nor proaporphines have been formed in this series of reactions.

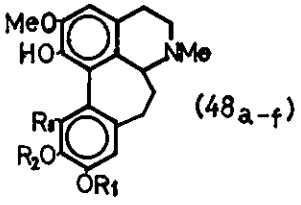
2. (±)-Homoaporphines, (±)-Homomorphinandienones, and (±)-Homoproaporphines

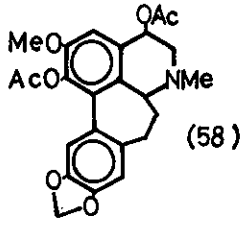
By use of conc. H_2SO_4 in Ac_2O, p-quinol acetates (41) from phenolic (±)-phenethyltetrahydroisoquinoline (38a) and (38c) gave (±)-O-acetylhomoaporphine (57a)[42] and (±)-O-acetylkreysigine (57c)[42] in 16 and 18% yield, respectively.



	R1	R2	R3
a	Me	Me	H
b	CH_2		H
c	Me	Me	OMe
d	Me	C_7H_7	H
e	C_7H_7	Me	H
f	Me	C_7H_7	OMe





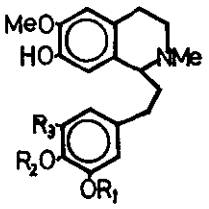
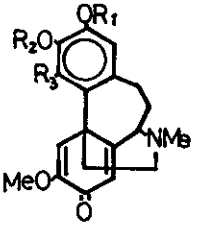
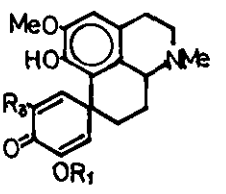


Acid hydrolysis of the latter furnished (±)-kreysigine (48c)[42,43] in 56% yield. Similarly, (±)-O-acetylhomoaporphine (57b)[36] was formed in 21.8% yield. In this

case, however, diastereomeric (±)-4-acetoxy-O-acetylhomoaporhines (58) were produced as by-products, though in low yields. Hydrolysis of (57a) and (57b) proceeded without difficulty giving (±)-homoaporphine (48a) and (48b).

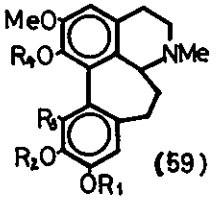
More conveniently, (48a), (48b) and (48c) were obtained in 52, 54.3, and 63% yield, respectively, by TFA treatment[44] of the corresponding p-quinol acetates (41).

On the other hand, when TFA in CH_2Cl_2 was employed as the cyclizing reagent, a markedly different result[44], except in the case of (48b), was uncovered; namely, (±)-homomorphinandienone (49) and (±)-homoproaporphine (50) besides homoaporphine

Starting Materials				Yields (%) of Products		
 (38)				 (48)	 (49)	 (50)
	R_1	R_2	R_3			
a	Me	Me	H	44.2	3.3	6.9
b	CH_2		H	55	—	—
c	Me	Me	OMe	35.2	23.1	31.3
d	Me	C_7H_7	H	39.3	6.1	15.5
e	C_7H_7	Me	H	29.6	0.3	11.4
f	Me	C_7H_7	OMe	27.3	12.2	15.9

(48) were formed as shown in the table.

Thus, (±)-O-benzylhomoaporphines (48d-f) and several (±)-homoaporphines (59a-f) including (±)-multifloramine (59e) were prepared in good yields using conventional reactions[44], hydrogenolysis with Pd on carbon or methylation with CH_2N_2 followed by hydrogenolysis.



(59)

	R_1	R_2	R_3	R_4
a	Me	H	H	H
b	H	Me	H	H
c	Me	H	H	Me
d	H	Me	H	Me
e	Me	H	OMe	H
f	Me	H	OMe	Me

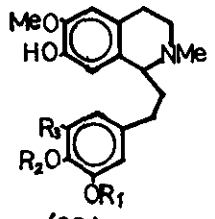
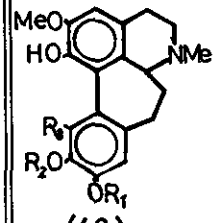
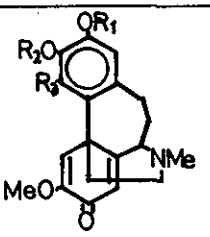
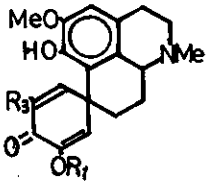
Coupled with Kametani's work[45], formation of (±)-O-benzylandrocymbine (49f) constitutes a formal synthesis of (±)-androcymbine (49, R_1=Me, R_2=H, R_3=OMe).

Surprisingly enough, (±)-homoproaporphines (50a) and (50d) from (38a) and (38d) were homogeneous and found to be the spiro-isomer of (±)-kreysiginone[43] on the basis of spectral data and melting point comparison. Mention of the mechanistic details, however, must be postponed until its absolute configuration is clarified.

Recently, Schwartz and coworkers[32a] have succeeded in preparing (±)-O-methylandrocymbine (49c) in 20% yield by TTFA oxidation of (38c). Accordingly, LTA oxidation[44] in the presence of TFA was deemed to give (49c) in one step.

In reality, (49c), (48c) and (50c) were produced in 26, 7.5 and 15% yield, respectively.

As compared to the case where p-quinol acetates (41) were treated with TFA in CH_2Cl_2, the yield of (±)-homomorphinandienone (49) was higher than that of (±)-homoaporphines (48) as shown in the table.

Starting Materials				Yields (%) of Products		
 (38)				 (48)	 (49)	 (50)
	R_1	R_2	R_3			
a	Me	Me	H	—	16	31
b	CH_2		H	19	—	—
c	Me	Me	OMe	7.5	26	15
d	Me	C_7H_7	H	—	14	18
e	C_7H_7	Me	H	—	5	16
f	Me	C_7H_7	OMe	10	13	10

As to the yield of (±)-homoproaporphines (50), there seemed no difference between these two methods. The present method, however, was of practical value in its selectivity allowing ready isolation of (49).

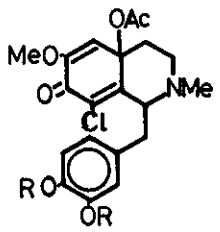
Though the mechanistic details of the reaction were not difinite the main reaction pathway seemed different from that

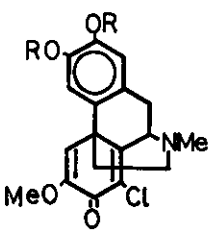
via a p-quinol acetate (41), in view of the fact[44] that treatment with a mixture of TFA and AcOH of the p-quinol acetate (41) gave eventually (49c), (48c), and (50c) in 13, 15, and 3% yield, respectively.

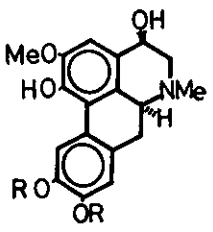
3. (±)-8-Chloro-morphinandienones and -homomorphinandienones

The above mentioned phenolic (±)-8-chloro-1-benzyltetrahydroisoquinolines (31)[22] seemed to be important starting materials for preparation of (44), since the presence of a chloro substituent at the 8-position would probably hinder the carbon-carbon coupling leading to (43) so that the coupling favorable to (44)[44] would result instead.

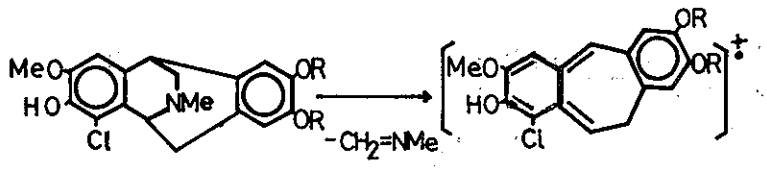
The p-quinol acetate (60a) of (31a) was treated with TFA at room temperature giving, after separation on preparative TLC, (±)-8-chloroamurine (61a) and (±)-1-chloroisopavine (62a) in 6.6 and 14.5% yield, respectively. The structure of the latter was deduced solely on the basis of the mass spectrum, which exhibited two characteristic peaks at m/e 318 and 316 due to ions (63a)[46] $(M^+ +2)-43$ and M^+-43, respectively.







(60) a R+R=CH_2 (61) (64)
b R=Me

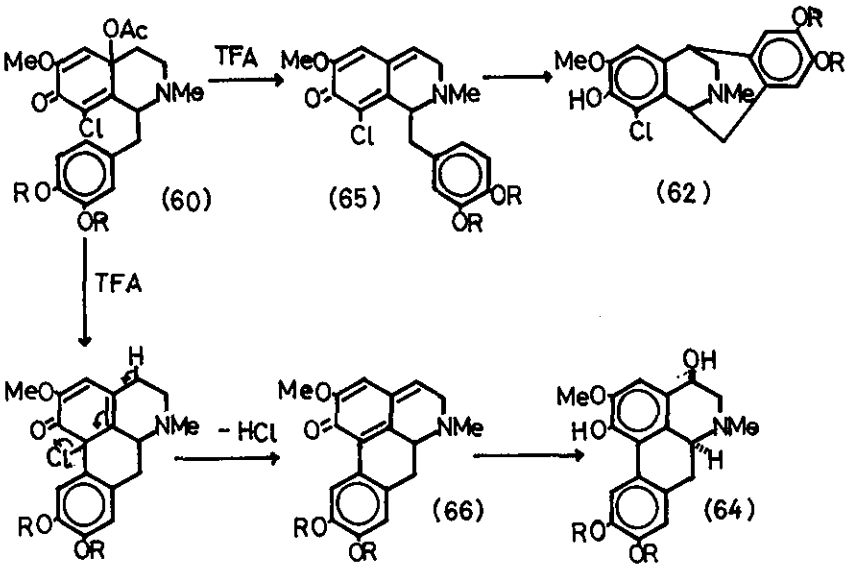


(62) (63)

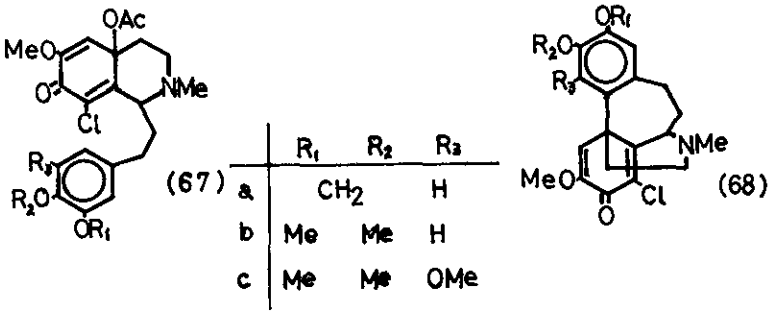
Similarly, the p-quinol acetate (60b) of (31b) gave (±)-8-chloro-O-methylflavinantine (61b) and (±)-4β-hydroxythaliporphine (64b) in 7.7 and 20% yield, respectively.

In these cases[44], both isopavines (62) and (±)-4-hydroxyaporphines [(64) and/or its diastereomer] were undoubtedly formed as clearly evidenced by mass spectrometry of the crude products. Isolation of these two, however, was severely precluded by the fact that several solvent systems did not cause effective separation displaying always one spot on TLC. Accordingly, recrystallization of these two could virtually lead to one component in a pure state. Thus, the protecting ability of the chloro substituent in the sense mentioned above was not important enough as to give a high yield of (61) contrary to our simple anticipation.

Intermediacy of two quinone methides such as (65) and (66) would be responsible for the formation of (62) and (64), respectively.



Likewise[44], p-quinol acetates (67) of phenolic (±)-8-chloro-1-phenethyltetrahydroisoquinolines (32a), (32b), and (32c) gave, when treated with TFA, (±)-8-chlorohomomorphinandienones (68a), (68b), and (68c) in 10, 18, and 26% yield, respectively.



	R_1	R_2	R_3
a	CH_2		H
b	Me	Me	H
c	Me	Me	OMe

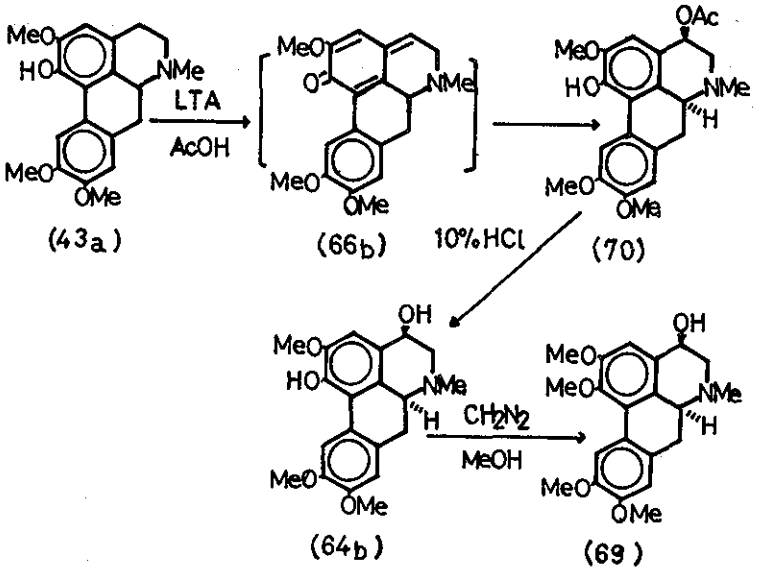
As stated above, LTA oxidation in the presence of TFA was also an improved method for the formation of (49). By this method[44], yields of (68b) and (68c) were actually increased up to 33 and 45% yield, respectively.

4. (±)-Cataline

(+)-Cataline (69)[47] is a 4-hydroxyaporphine isolated from Glaucium flavum Cr. var. vestitum.

As described above, the fact[34] that (±)-4-acetoxy-O-acetylthaliporphine (54a) was formed though in low yield, prompted us to search for a better route to secure the compound, which must be a key intermediate leading to (69). On the other hand, LTA oxidation of (43a) was a matter of concern, in order to extend the scope of the present reaction.

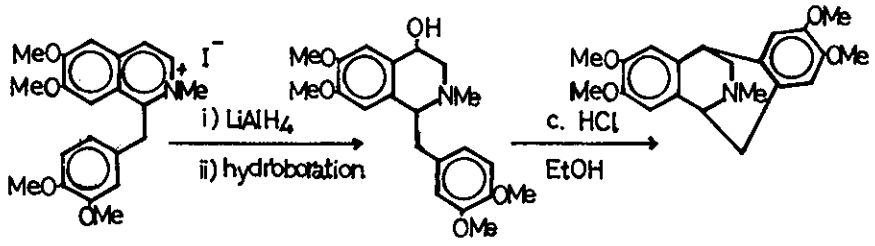
Thus, (±)-thaliporphine (43a) was oxidized in AcOH at room temperature of give (±)-4β-acetoxythaliporphine (70)[48] in quantitative yield. Stereospecific introduction of the acetoxyl group in the quinone methide (66b) probably occurred by the participation of nitrogen lone pair electrons with the incoming AcOH molecule.



Quantitative hydrolysis of (70) was achieved with 10% HCl at room temperature furnishing (64b). On methylation with CH_2N_2, (±)-cataline (69) was synthesized in 86.5% yield.

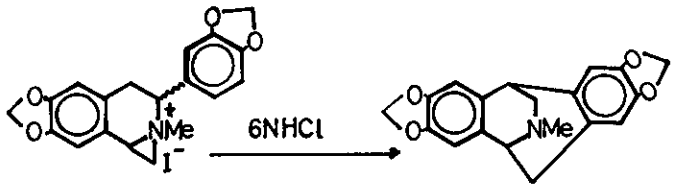
5. Isopavines

Since Kupchan's confirmation[49] of the structure (46) of isopavine by synthesis, further syntheses have been accomplished. By use of a standard method, Dyke[50] prepared the 4-hydroxy-tetrahydroisoquinoline (72) from the methiodide (71). Subsequent acid treatment of (72) then afforded (±)-O-methylthalisopavine (73)[49].



(71) (72) (73)

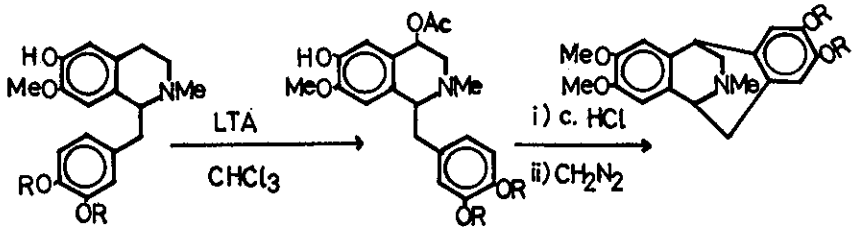
Another ingeneous approach has been announced by Kametani and coworkers[51], who synthesized (±)-reframidine (75)[50] starting from the aziridinium salt (74).



(74) (75)

In consideration of these achievements, the ready accessibility of (±)-4-acetoxy-6-hydroxy-7-methoxytetrahydroisoquinolines (35)[23] described above is suggestive of their potential utility for the synthesis of isopavine (46) or homoisopavine (51) alkaloids. Thus, 1-(3',4'-dimethoxy- and 3',4'-methylenedioxy)-benzyl-6-tetrahydroisoquinolinols [(78a) and (78b)] were oxidized in fair yields to their corresponding 4-acetoxy derivatives [(79a) and (79b)], acid treatment of which (conc. HCl in EtOH) followed by methylation with CH_2N_2 left

(±)-O-methylthalisopavine (73)[49,50,52] and (±)-reframine (80)[50,52], respectively. Yields in the cyclization step amounted to 90-92% and reaction time was appreciablly shortened as anticipated. The cyclization was confirmed to be equally effected by TFA. Similar sequence of reactions on (±)-1-phenethyl-6-tetrahydroisoquinolinols of this series resulted in the formation of homoisopavines (51)[53].



(78) a R = Me (79) (73) R = Me

b R+R = CH_2 (80) R+R = CH_2

Conclusion

Two kinds of tetrahydroisoquinolinols can readily be oxidized with LTA, according to their oxygenation pattern, giving p-quinol acetates or 4-acetoxytetrahydroisoquinolinols, from which several isoquinoline alkaloids are shown to be easily prepared.

Thus, it is evident that LTA is a reagent of choice in the synthesis of isoquinoline alkaloids.

ACKNOWLEDGEMENT The authors are deeply indebted to the Ministry of Education for partial financial support of this work. They are also grateful to Professor T. Kametani of Tohoku University for copies of spectral charts of several alkaloids, and to Professors L. Castedo of University of Bilbao and I. Ribas of University of Santiago for identification of (±)-cataline. Thanks are also due to Dr. T. Moroe of Takasago Perfumery Co., Ltd. for his kind gift of starting materials.

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Received, 2nd September, 1975