

FORMATION OF MORPHINANDIENONES VIA *o*-QUINOL ACETATES OF N-TRI-
FLUOROACETYLTETRAHYDROISOQUINOLIN-7-OLS[†]

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Abstract-- (±)-N-Trifluoroacetylnormorphinandienones (**4a,b**) were
obtained by acid treatment of *o*-quinol acetates [*o*-QAs] (**2a,b**)
in CH₂Cl₂ or CH₃CN at low temperature.

As part of our continuing study on application¹ of lead tetraacetate [Pb(OAc)₄] oxidation to synthesis of isoquinoline alkaloids, we have previously² reported

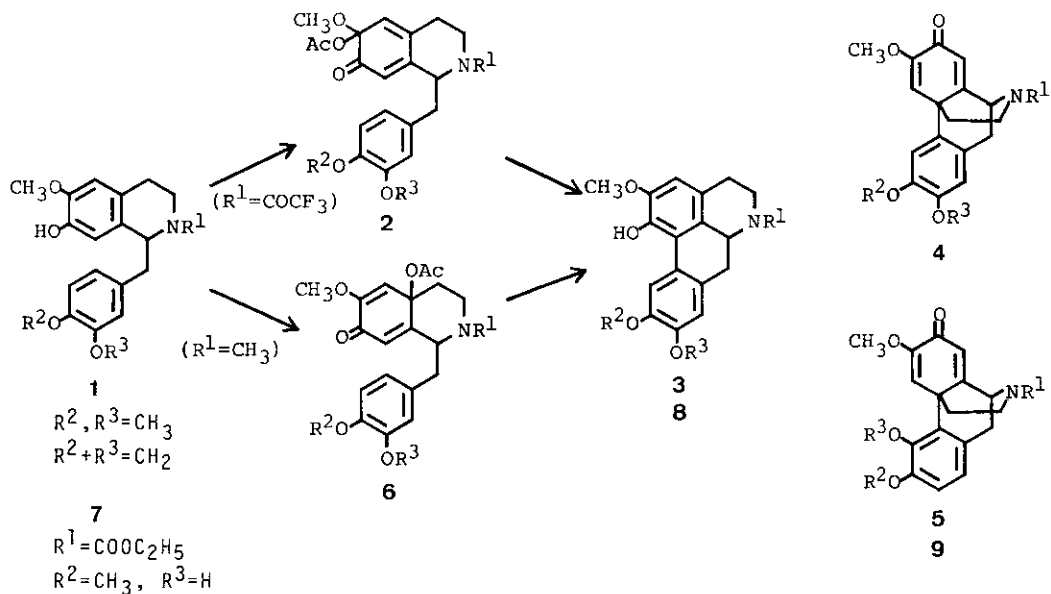


Chart 1

[†] This paper is dedicated in the memory of Professor Tetsuji Kametani.

that $\text{Pb}(\text{OAc})_4$ oxidation of ($\pm$)-N-trifluoroacetyltetrahydroisoquinolin-7-ols (**1**) gives rise to unexpectedly stable N-trifluoroacetyl o-quinol acetates [o-QAs (**2**)] in almost quantitative yield, which are treated with trifluoroacetic acid [CF_3COOH] to afford the corresponding aporphines (**3**). In the reaction, however, none of *para-para* or *para-ortho* coupling products such as morphinandienones (**4** or **5**) have been obtained as well as in reaction of N-methyl *p*-QA^{3,4} (**6** : $\text{R}^1=\text{Me}$), while the similar oxidation of N-ethoxycarbonyltetrahydroisoquinolin-7-ol (**7** : $\text{R}^1=\text{COOC}_2\text{H}_5$) in CH_2Cl_2 in the presence of trichloroacetic acid at -25°C ⁵ gives *para-ortho* coupling product, N-ethoxycarbonylnorsalutaridine (**9**), together with aporphine (**8**). In order to examine the possibility of the formation of morphinandienones, therefore, acid treatment of o-QAs (**2**) under a variety of conditions was carried out. In the present paper, we wish to report a first synthesis of morphinandienones (**4**) via N-trifluoroacetyl o-QAs (**2**).

CF_3COOH (0.5 ml) was added dropwise at 0°C to a stirred solution of o-QA (**2a**) in CH_2Cl_2 (10 ml), prepared from **1a** (100 mg),² and the mixture was stirred for 3 min. Usual work-up of the reaction mixture gave an oil, which was purified on preparative thin-layer chromatography [silica gel 60 F_{254} (Merck) ; developing solvent ; AcOEt : hexane = 2 : 1] to afford **3a**² (74.2 mg, 74%) and **4a**^{6,7} (16.3 mg, 16%), respectively. Physical and spectral data of **4a** were in good agreement with those reported in literature.⁸ This finding suggested that **4a** could be formed in the reaction of o-QA (**2a**) at lower temperature. Nevertheless, similar reaction at -46°C did not improved yield of **4a**. Therefore, acetonitrile, more polar and aprotic solvent, instead of CH_2Cl_2 was used. The similar reaction of **2a** in CH_3CN at 0°C gave **4a** and **3a** in a ratio of about 1:1.15. Furthermore, at -25°C the formation of **4a** was superior to **3a**.⁹

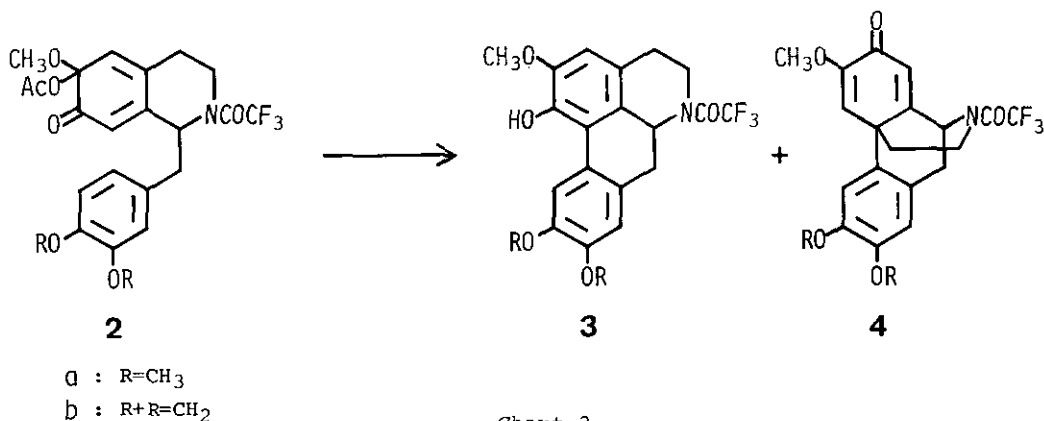


Chart 2

The similar tendency was also observed in the reaction of 2b. The results are summarised in Table I.

Table I. Acid-catalysed Reaction of *o*-QAs (2)

<i>o</i> -QAs 2	Reaction Conditions			Product			
	Solvent	Temp.* (°C)	Time (min)	3 Yield (%)	4 Yield (%)	4 Yield (%)	
a	CH ₂ Cl ₂	0	3	a 74	a 16		
a**	CH ₂ Cl ₂	-46	60	a 74	a 20		
a	CH ₃ CN	0	2	a 46	a 40		
a	CH ₃ CN	-25	5	a 42	a 46		
b**	CH ₂ Cl ₂	-46	60	b 59	b 18		
b	CH ₃ CN	-30	3	b 18	b 52		

* Bath Temperature

** A solution of CF₃COOH(1 ml) in CH₂Cl₂(10 ml), which was cooled at -46°C, was added in one portion to a solution of 2 in CH₂Cl₂ (10 ml) at the same temperature.

It is noteworthy that a first synthesis of morphinandienones (4a,b) was accomplished via N-trifluoroacetyl *o*-QAs(2), although the reason why CH₃CN was more effective than CH₂Cl₂ in formation¹⁰ of 4a,b via N-trifluoroacetyl *o*-QAs (2) is inexplicable. Further investigation on the mechanistic pathway is in progress.

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 4. $\text{Pb}(\text{OAc})_4$ oxidation of 8-chlorocodamine in a mixture of CF_3COOH and CH_2Cl_2 gives 8-chloromorphinandienone accompanied by both aporphine and 8-chloroisopavine, though in low yield ; H. Hara, O. Hoshino, and B. Umezawa, Nippon Kagaku Kaishi, 1981, 813.
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 6. All new compounds described in this report gave satisfactory elemental and mass spectral analyses.
 7. Ir spectra were taken with a Hitachi 260-10 spectrophotometer in CHCl_3 solution. ^1H -Nmr spectra were measured with a JEOL-JNM-FX-100[100MHz] instrument in CDCl_3 solution using TMS as internal standard. **4a** : mp 177-179°C(ether) [lit.⁸ mp 179.5-181.5°C(ether)] ; δ (ppm) : 3.80, 3.86, 3.90 (9H, each s, 3xOMe), 6.33-6.39 (2H, m), 6.60, 6.82 (2H, each s, olefinic H) ; ν : 1670, 1645, 1620 cm^{-1} . **4b** : mp 210-211°C(benzene-isopropyl ether) ; δ (ppm) : 3.80(3H, s, OMe), 5.92-5.96 (2H, m), 6.27(1H, s), 6.34, 6.38(1H, each s), 6.59(1H, s), 6.85(1H, s) ; ν : 1690, 1670, 1645, 1620 cm^{-1} ; m/z : 407(M^+).
 8. S. M. Kupchan, O. P. Dhingra, and C-K. Kim, J. Org. Chem., 1978, 43, 4076.
 9. Other polar solvents such as dimethylformamide, nitromethane, acetone, and ethyl acetate gave unsatisfactory results.
 10. Although the reactivity of N-trifluoroacetyl o-QAs (**2**) could not be compared exactly with that of N-methyl p-QAs (**6**), a lone pair of nitrogen atom seemed to play a significant role in the formation of morphinandienones.

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