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FORMATION OF MORPHINANDIENONES VIA *o*-QUINOL ACETATES OF N-TRIFLUOROACETYLTETRAHYDROISOQUINOLIN-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 CH_2Cl_2 or CH_3CN at low temperature.

As part of our continuing study on application[1] of lead tetraacetate [$Pb(OAc)_4$] oxidation to synthesis of isoquinoline alkaloids, we have previously[2] reported

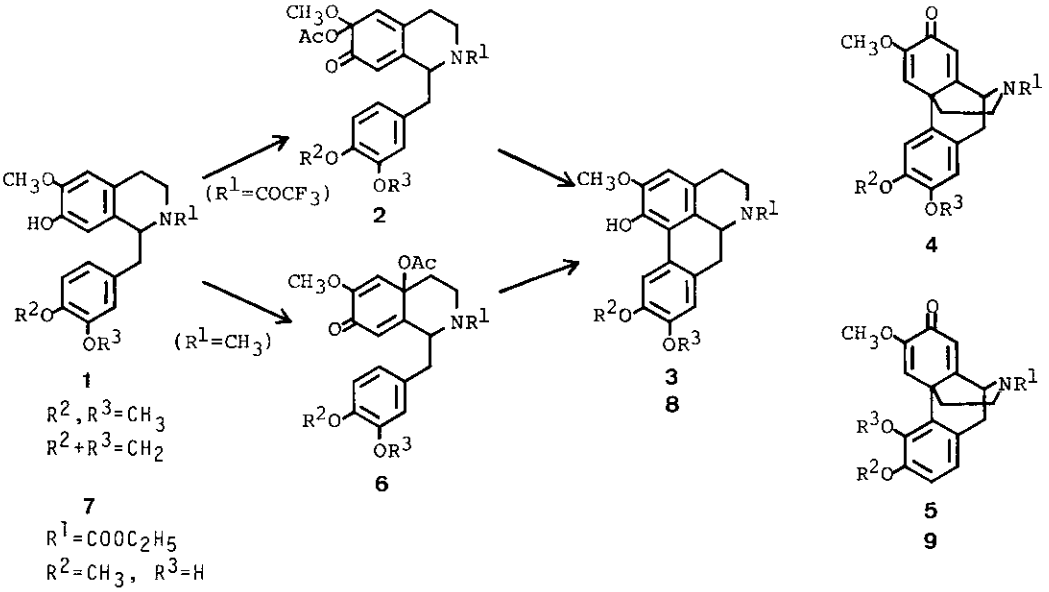

Chart 1

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

that $Pb(OAc)_4$ oxidation of *(±)-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** : R^1=Me), while the similar oxidation of N-ethoxycarbonyltetrahydroisoquinolin-7-ol (**7** : $R^1=COOC_2H_5$) 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) ; developping 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]

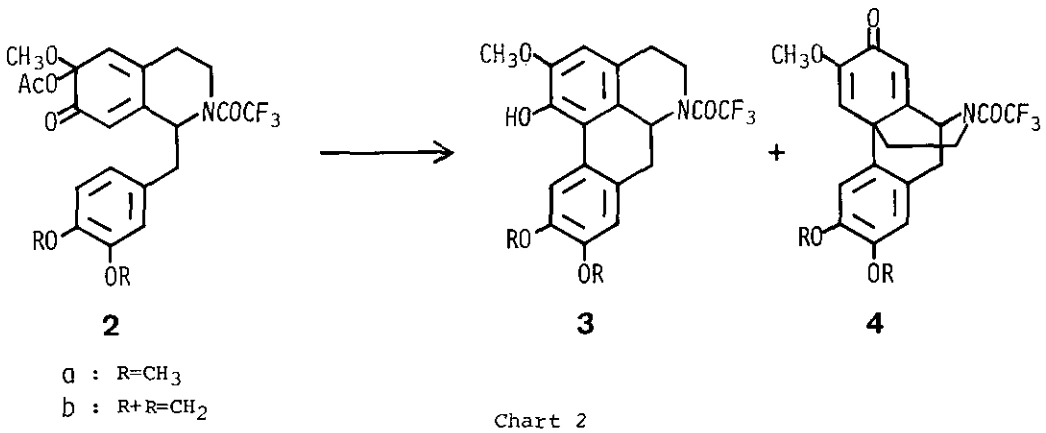

Chart 2

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

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

o-QAs	Reaction Conditions			Product			
2	Solvent	Temp.* (°C)	Time (min)	**3**	Yield (%)	**4**	Yield (%)
a	CH_2Cl_2	0	3	**a**	74	**a**	16
a**	CH_2Cl_2	-46	60	**a**	74	**a**	20
a	CH_3CN	0	2	**a**	46	**a**	40
a	CH_3CN	-25	5	**a**	42	**a**	46
b**	CH_2Cl_2	-46	60	**b**	59	**b**	18
b	CH_3CN	-30	3	**b**	18	**b**	52

* Bath Temperature

** A solution of CF_3COOH(1 ml) in CH_2Cl_2(10 ml), which was cooled at -46°C, was added in one portion to a solution of **2** in CH_2Cl_2 (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 CH_3CN was more effective than CH_2Cl_2 in formation[10] of **4a,b** via N-trifluoroacetyl *o*-QAs (**2**) is inexplicable. Further investigation on the mechanistic pathway is in progress.

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3. H. Hara, O. Hoshino, and B. Umezawa, *Chem. Pharm. Bull.*, 1976, **24**, 262.
4. $Pb(OAc)_4$ 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, *Nipppon Kagaku Kaishi*, **1981**, 813.
5. Cs. Szántay, G. Blaskó, M. Bárczai-Beke, P. Péchy, and G. Dörnyei, *Tetrahedron Lett.*, 1980, **21**, 3509.
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. ^{1}H-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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