ACID-CATALYZED REACTION OF 1-SUBSTITUTED 10-ACETOXY-8-CHLORO-6-METHOXY-2-METHYL-7-OXO-$\Delta^{5,6,8,9}$-HEXAHYDROISOQUINOLINES✦

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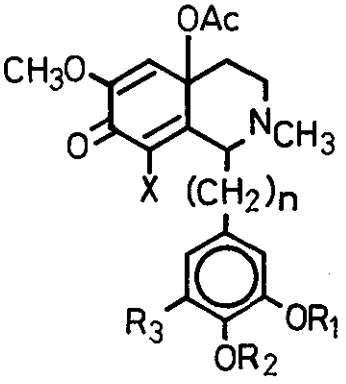
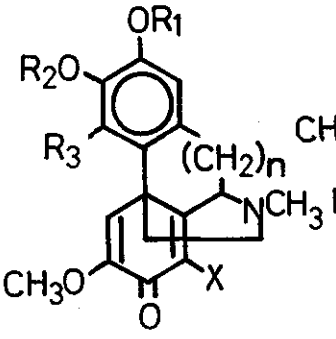
Treatment with trifluoroacetic acid of the p-quinol acetates (VIa, b) derived from 1-benzyl-8-chlorotetrahydroisoquinolines (Va, b) gave the corresponding 8-chloromorphinandienones (VIIa, b), 1-chloroisopavines (VIIIa, b), and 4-β-hydroxy-aporphines (IXa, b), respectively. By similar reaction of p-quinol acetates (XIIIa-c), 8-chloro-homomorphinandienones (XIVa-c), 1-chlorohomo-isopavines (XVa-c), and 4β-hydroxyhomoaporphines (XVIa, b) were yielded, respectively.

Some years ago we anticipated that p-quinol acetates (I) would on acid treatment give rise to morphinandienones (II) and/or isopavines (III).

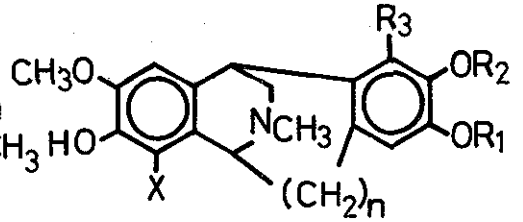
✦ Dedicated to Dr. K. Takeda on the occasion of his seventieth birthday.



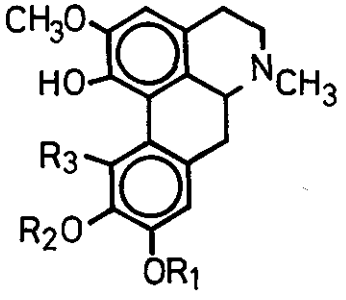
I : n=1 , X=H
VI : n=1 , X=Cl
XI : n=2 , X=H
XIII : n=2 , X=Cl



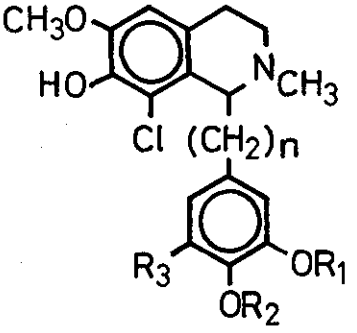
II : n=1 , X=H
VII : n=1 , X=Cl
XII : n=2 , X=H
XIV : n=2 , X=Cl



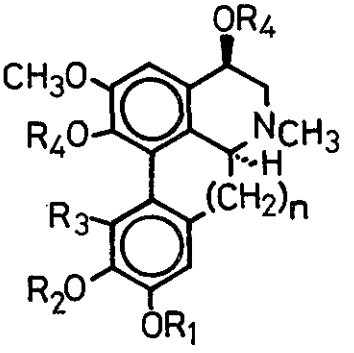
III : n=1 , X=H
VIII : n=1 , X=Cl
XV : n=2 , X=Cl



IV



V : n=1
XVII : n=2



IX : n=1 , R_4=H
X : n=1 , R_4=Ac
XVI : n=2 , R_4=H

a : $R_1 + R_2 = CH_2$, R_3=H
b : $R_1 = R_2 = CH_3$, R_3=H
c : $R_1 = R_2 = CH_3$, $R_3 = OCH_3$

Contrary to the anticipation, however, none of them could be produced since then. The only products prepared by the method always remained to aporphines (IV)[1] in spite of numerous attempts.

Therefore, to solve the problem, a little modification of the starting material seemed necessary. Namely, if an assumption that the C-C coupling reaction leading to aporphines and that to morphinandienones and/or isopavines were in competition was valid, blocking of the C-8 position by chlorine atom would hinder the former and in turn favor the latter to a certain degree.

Thus, lead tetraacetate oxidation of 8-chloro-7-phenolic tetrahydroisoquinolines (V)[2] and subsequent acid treatment were carried out with the following results.

The oxidation with the oxidant (270 mg) of Va (200 mg) in acetic acid (2 ml) at room temperature for 30 min. gave a diastereomeric mixture of p-quinol acetates (VIa) [IR[3] ν_{max} cm^{-1}: 1730 ($OCOCH_3$), 1690, 1670, 1650 (dienone)] (260 mg, oil), which without purification was treated with trifluoroacetic acid (CF_3CO_2H) for 10 min. at room temperature. Usual work-up of the reaction mixture afforded an amorphous mass (228 mg), whose separation on preparative t.l.c.[4] ($CHCl_3$: MeOH=10:1) gave two fractions A (52 mg) and B (39 mg). Fraction A was further purified by alumina column chromatography[5] giving a crystalline compound, (±)-8-chloroamurine (VIIa) (11 mg, 6%), mp 188-189° (MeOH)[6]. N.m.r.[7] ($CDCl_3$) δ: 2.42 (3H, s, NCH_3), 3.77 (3H, s, OCH_3), 4.43 (1H, b.d., J=5Hz, 9-H), 5.91 (2H, m, OCH_2O), 6.33, 6.59, 6.80 (each 1H, s, 2 x aromatic H and 1 x olefinic H); i.r. ν_{max} cm^{-1}: 1665,

1655 (sh), 1650 (sh) (dienone); m.s.[8] m/e: 361 (M^++ 2), 359 (M^+). To this compound was assigned the expected structure (VIIa) having morphinandienone skeleton. Fraction B was separated through preparative t.l.c. (AcOEt: iso-PrOH = 1:1) to afford two crystalline compounds. The less polar compound (VIIIa) [13 mg, 7%; mp 234-236°; n.m.r. (pyridine-d_5) δ: 2.45 (3H, s, NCH_3), 3.69 (3H, s, OCH_3), 4.57 (1H, t, J = 4Hz, 12-H), 5.87 (2H, m, OCH_2O), 6.55, 6.77, 6.88 (each 1H, s, aromatic H)] was assigned as 1-chloroisopavine on the basis of elemental analysis and mass spectrum. Mainly because, a series of four peaks [m/e: 359 (M^+), 358 ($M^+ - 1$), 316 ($M^+ - 43$), 224 ($M^+ - 135$; base peak)] in the mass spectrum were indicative of an isopavine skeleton[9] and another four (m/e: 361, 360, 318, 226), which had approximately one-third intensity of the former, clearly showed the presence of one chlorine atom in the molecule. On the other hand, the more polar compound (IXa) (11 mg, 6%), mp 195-206° (dec.), which was unstable to heat, was acetylated (Ac_2O-pyridine) giving a diacetate (Xa), mp 190-192°. This diacetate was consistent with an authentic sample of (±)-4β-acetoxy-O-acetyldomesticine[1b] by both mixed fusion and i.r. comparison. Accordingly, the structure of IXa was proved to be (±)-4β-hydroxydomesticine.

Similar reaction of the p-quinol acetate (VIb) obtained from Vb gave (±)-8-chloro-O-methylflavinanthine (VIIb), (±)-1-chloroisopavine (VIIIb), and (±)-4β-hydroxythaliporphine (IXb)[10], in 3, 4, and 23% yield, respectively.

Although homomorphinandienones (XIIb, c)[11] were already synthesized by treatment with CF_3CO_2H of the corresponding p-quinol acetates (XIb, c), their yields were low (3 and 23%)

and XIIa was never formed.

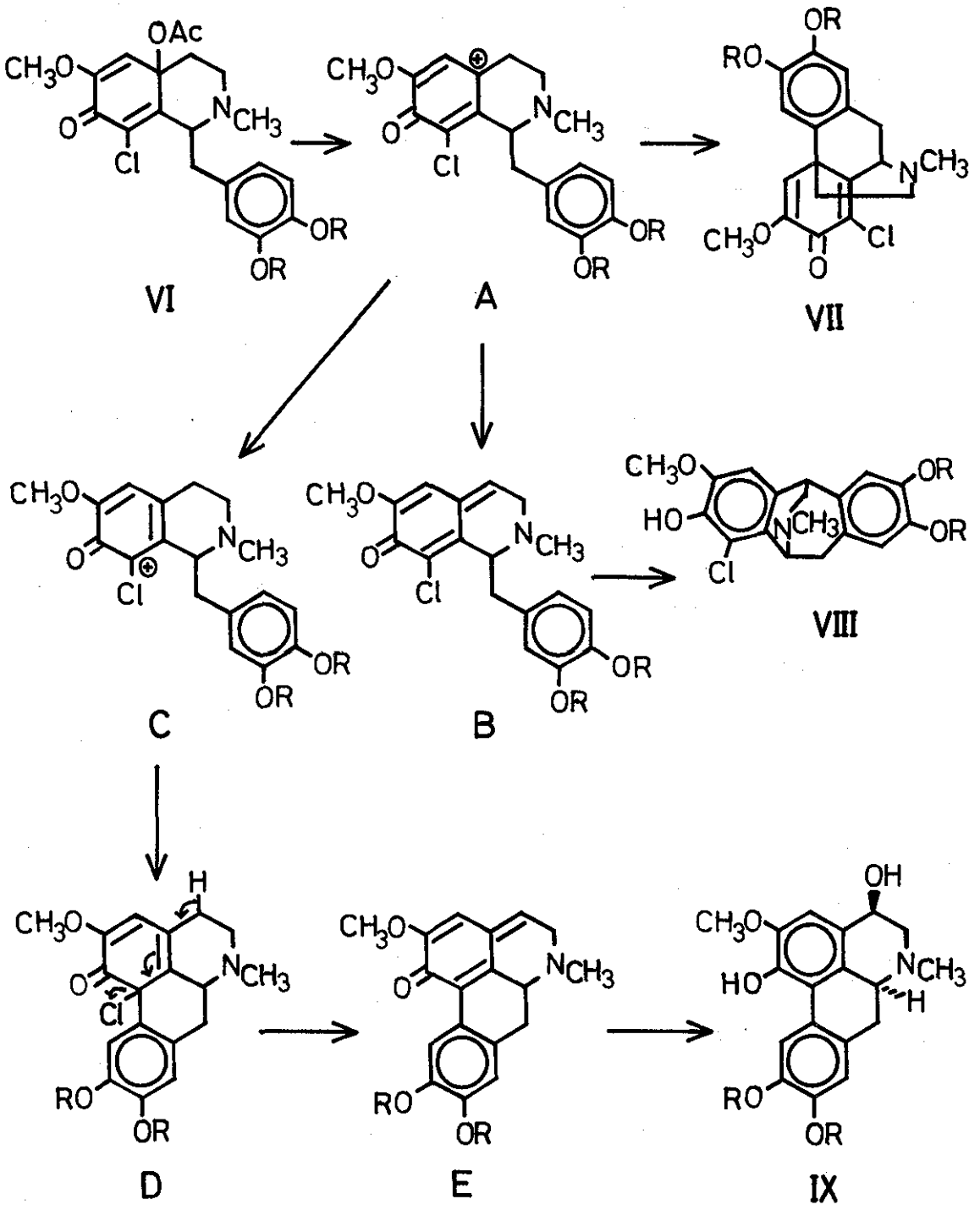
Preparation of 8-chlorohomomorphinandienones (XIVa-c), therefore, seemed interesting to confirm the assumption mentioned above. Treatment with CF_3CO_2H of the p-quinol acetates (XIIIa-c) gave XIVa-c along with appreciable amounts of homoisopavines (XVa-c) and 4β-hydroxyhomoaporphines (XVIa, b). The yields of XIVa-c were expectedly higher than those in the case of XIIa-c as listed in Table 1. Structures of these products were deduced on the basis of spectral data.

A presumptive mechanistic pathway leading to these three was visualized in Scheme 1. Namely, leaving of acetoxyl group at the C-10 position gave first an allylic carbonium cation (A), which on one hand was transformed to a quinone methide (B) and on the other to another cation (C) through isomerization.

Starting Materials	Yields (%) of Products		
Va	VIIa (6) mp 188-189°	VIIIa (7) mp 234-236°	IXa (6) (mp 190-192°)[a]
Vb	VIIb (3) mp 192-193°	VIIIb (4) mp 225-227°	IXb (23) (mp 245-246°)[a]
XVIIa	XIVa (11) mp 214-215°	XVa (16) mp 173-177°	XVIa (17) (mp 192-194°)[a]
XVIIb	XIVb (18) mp 174-175°	XVb (17) mp 215-217°	XVIb (30) (mp 235-236°)[b]
XVIIc	XIVc (31) mp 169-170.5°	XVc (9) mp 173-174°	———

[a] Diacetate
[b] Methiodide of diacetate

Table 1



Scheme 1

Intramolecular nucleophilic attack of A and B gave rise to morphinandienone (VII) and isopavine (VIII), respectively. The same attack of C gave an intermediate such as D, which on dehydrochlorination must afford another quinone methide (E) due to its strained nature. Conjugate addition to E with water molecule or its equivalent gave 4β-hydroxyaporphine (IX).

Thus, it was proved that the early anticipation was reasonable though not exclusively and that chlorine atom as protecting group was not so effective as to alter the entire reaction course.

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2. H. Hara, O. Hoshino, and B. Umezawa, Heterocycles, 1975, 3. 123.
3. I.r. spectra were run on a Hitachi 215 spectrometer in $CHCl_3$.
4. Preparative t.l.c. was run on silica gel HF_{254} (Merck).
5. Column chromatography was performed on Aluminum Oxide neutral Woelm (Woelm); eluant: $CHCl_3$.

6. All new compounds gave satisfactory analytical data.

7. N.m.r. spectra were taken with a Japan Electron Optics Labs. Model JNR-4H-100 spectrometer in $CDCl_3$ on pyridine-d_5 solution (5-10%) by using tetramethylsilane as internal standard.

8. Mass spectra were measured with a Hitachi Model RMU-6E mass spectrometer.

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