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Studies on Tetrahydroisoquinolines. II.[1] An Acid-Catalysed Alcoholysis of 10-Acetoxy-6-methoxy-2-methyl-7-oxo-$\Delta^{5,6,8,9}$-hexahydroisoquinoline (*p*-Quinol Acetate)

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Acid-catalysed (BF_3-etherate or conc. H_2SO_4) reaction of *p*-quinol acetate (IVa) in various alcohols at room temperature gave the corresponding 6, 10-dialkoxy and 6-methoxy-10-alkoxy products [(VI) and (VII)], mainly.

Essential feature of the reaction was infered to be stereochemically controlled allylic addition of alcohols to 6- or 10-position in IVa.

It has been widely known that acid treatment[3] of *p*-quinols or their acetates gives the products which resemble dienone-phenol type rearrangement ones. For instance, reaction of *p*-quinol acetate[4] (I) derivable from 7-tetralol (II) with acetic anhydride (Ac_2O) in the presence of conc. H_2SO_4 affords 5,7-diacetoxytetraline (III) as a sole product. However, similar treatment[1] of 10-acetoxy-6-methoxy-2-methyl-7-oxo-$\Delta^{5,6,8,9}$-hexahydroisoquinolines (*p*-quinol acetates) (IVa—d) as noted in I has been found to furnish only the corresponding 4,7-diacetoxy-6-methoxy-2-metlyl-1,2,3,4-tetrahydroisoquinolines (Va—d), in which a newly introduced acetoxy group is not at 5- but 4-position. This is quite different from the result[4] in the case of I. As described previously,[1] such a remarkable difference between rearrangement mode of I and that of IV is supposedly attributable to the effect not only of 6-methoxy but nitrogen atom in IV.

From the above finding, the authors now directed their attention to a chemical behavior of IVa under acidic conditions. In general, reaction of *p*-quinols or their acetates is carried out in Ac_2O containing conc. H_2SO_4 or boron trifluoride (BF_3)-etherate. Though less uncommon,[5] however, reaction in methyl or ethyl alcohol instead of Ac_2O also is known. Then reaction of IVa in various alcohols containing BF_3-etherate or conc. H_2SO_4 was carried out and the following result was obtained.

A methanolic solution of IVa in the presence of BF_3-etherate was stirred for 0.5 hr at room temperature. Usual work-up of the reaction mixture afforded an oil, chromatography of which over silicic acid (Mallinckrodt) gave colorless prisms of VIa, mp 112—113°, in 40% yield. Nuclear magnetic resonance (NMR) spectrum of VIa showed each three proton singlet at τ 6.95 and 6.26 for aliphatic and aromatic methoxy groups and each one proton singlet at τ 4.44 and 3.68 for C-8 and C-5 hydrogen. Its infrared (IR) spectrum (KBr) displayed a characteristic absorption band due to a dienone group at 1675, 1645 and 1625 cm^{-1}.

From the above spectral data and elemental analysis, structure of VIa was assumed to be 6,10-dimethoxy-2-melthyl-7-oxo-$\Delta^{5,6,8,9}$-hexahydroisoquinoline.

It was thus found that replacement of 10-acetoxy group with methoxy group readily took place without any change of the dienone moiety in IVa.

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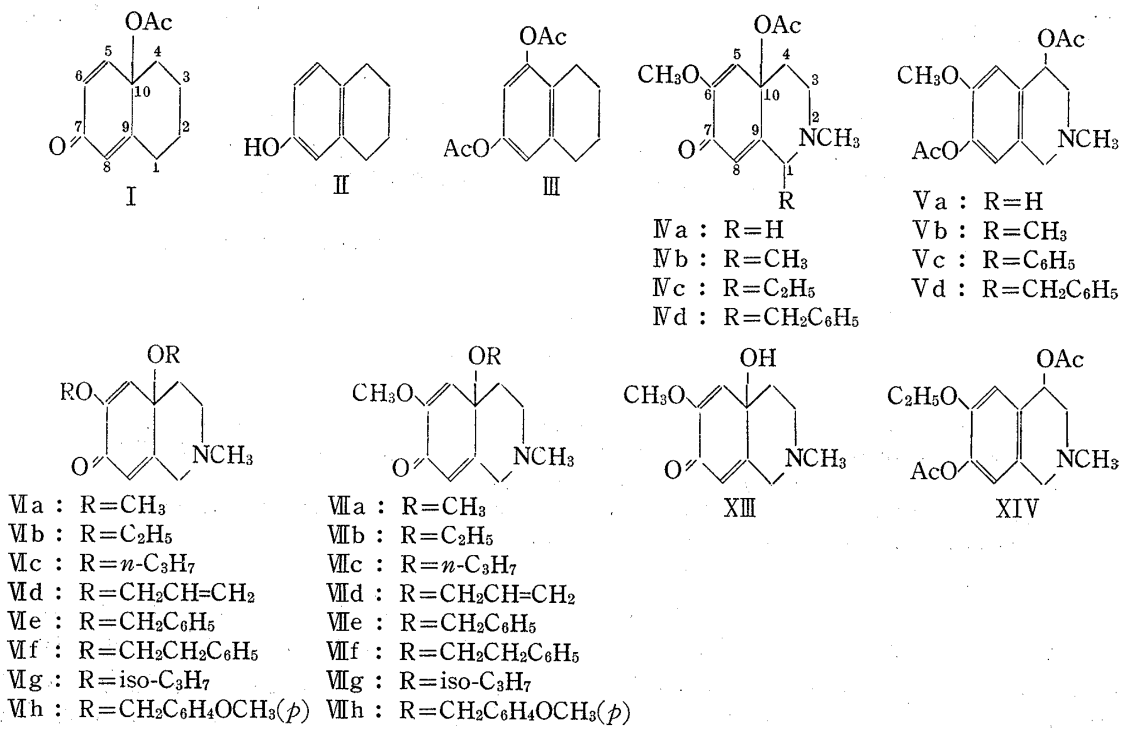
1) Part I: B. Umezawa, O. Hoshino, Y. Terayama, K. Ohyama, Y. Yamanashi, T. Inoue and T. Toshioka, *Chem. Pharm. Bull.* (Tokyo), **19**, 2138 (1971).

2) Location: *12, Ichigaya-funagawara-machi, Shinjuku-ku, Tokyo, 162, Japan.*

3) B. Miller, "Mechanisms of Molecular Migrations," Vol. 1, ed. by B.S. Thyagarajan, Interscience Publishers, Inc., New York, 1968, p. 219.

4) S. Goodwin and B. Witkop, *J. Am. Chem. Soc.*, **79**, 179 (1957).

5) E. Bamberger, *Ber.*, 33, 3618 (1900); *idem, Ann.*, **390**, 164 (1912).



I II III

IVa : R=H
IVb : R=CH_3
IVc : R=C_2H_5
IVd : R=$CH_2C_6H_5$

Va : R=H
Vb : R=CH_3
Vc : R=C_6H_5
Vd : R=$CH_2C_6H_5$

VIa : R=CH_3
VIb : R=C_2H_5
VIc : R=n-C_3H_7
VId : R=$CH_2CH{=}CH_2$
VIe : R=$CH_2C_6H_5$
VIf : R=$CH_2CH_2C_6H_5$
VIg : R=iso-C_3H_7
VIh : R=$CH_2C_6H_4OCH_3(p)$

VIIa : R=CH_3
VIIb : R=C_2H_5
VIIc : R=n-C_3H_7
VIId : R=$CH_2CH{=}CH_2$
VIIe : R=$CH_2C_6H_5$
VIIf : R=$CH_2CH_2C_6H_5$
VIIg : R=iso-C_3H_7
VIIh : R=$CH_2C_6H_4OCH_3(p)$

XIII XIV

Chart 1

Based on the fact, similar treatment of IVa in ethyl alcohol was undertaken. Usual work-up of the reaction mixture followed by chromatography gave colorless prisms of VIb,[6] mp 76—78°, in 44% yield. In its NMR spectrum, each three proton triplet (J=7.0 Hz) for each ethoxy methyl protons and each two proton quartet (J=7.0 Hz) for each ethoxyl methylene protons appeared at τ 8.84 and 8.56; 6.74 and 6.09, respectively. The IR spectrum indicated an absorption band for a dienone group at 1675, 1650 and 1625 cm^{-1}.

These spectral data and elemental analysis clearly supported that structure of VIb was 6,10-diethoxy-2-methyl-7-oxo-$\Delta^{5,6,8,9}$-hexahydroisoquinoline.

In the same reaction, formation of 10-ethoxy-6-methoxy-2-methyl-7-oxo-$\Delta^{5,6,8,9}$-hexahydroisoquinoline (VIIb) as a by product was observed by NMR spectrum of the product, but VIIb could not be isolated as pure state.

Thus, surprisingly it was shown that not only 10-acetoxy but 6-methoxy group was smoothly replaced with ethoxy group and the dienone part remained.

From the above finding that VIIb was formed besides VIb though not isolable, the reaction appeared to be influenced by the steric effect of alkyl chain in alcohols used. In consequence, it was expected that if alcohols having long and/or branching alkyl chain were used, yield of the product would decrease and at the same time the product ratio (6,10-dialkoxy to 10-monoalkoxy product) would approach to or be below 1.

In view of this point, similar reaction of n-propyl alcohol was performed. Usual work-up of the reaction mixture and chromatography furnished an oil of VIc (picrate, mp 149—150.5°) in 28% yield and colorless prisms of VIIc, mp 87—88° (n-hexane), in 6% yield. NMR spectrum of the former showed each triplet (J=7.5 Hz) at τ 9.09 and 8.98 for two n-propoxyl methyl protons and a triplet (J=7.5 Hz) at τ 6.23 for an olefinic n-propoxyl methylene pro-

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6) The finding that lead tetraacetate oxidation of 7-tetralol (I) in alcohols (MeOH, EtOH or n-BuOH) containing BF_3-etherate gives the corresponding p-quinol ethers in 49.0, 12.0 or 9.5% yield has been reported by E. Hecker and R. Lattrell [*Ann.*, **662**, 48 (1963)]. However, the similar lead tetraacetate oxidation of IVa in EtOH gave only a mixture of VIb and VIIb (2:1) in much lower yield than that in the present reaction. The product ratio was calculated by measuring each peak area due to olefinic $-OCH_2CH_3$ and $-OCH_3$ group in NMR spectrum.

tons. That of the latter displayed a triplet (J=7.5 Hz) at τ 9.08 for a n-propoxyl methyl protons and a singlet at τ 6.27 for an olefinic methoxyl methyl protons.

From each NMR spectrum and elemental analysis, it was supposed that structures of VIc and VIIc were 6-n-propoxy- and 6-methoxy-2-methyl-10-n-propoxy-7-oxo-$\Delta^{5,6,8,9}$-hexahydroisoquinoline, respectively.

Thus the assumption would be acceptable. However, further confirmation seemed to be necessary by examining the reaction in other alcohols. Then, analogous treatments with allyl, benzyl, β-phenethyl or iso-propyl alcohol were undertaken and the result was shown in Table I.

Table I. Melting Point, Yield and Elemental Analysis of VI and VII (in the Presence of BF_3-etherate)

Solvent	Compound	mp (°C)	Yield (%)	Formula	Analaysis (%) Calcd. C	H	N	Found C	H	N
MeOH	VIa (=VIIa)	112—113	40	$C_{12}H_{17}O_3N$	64.55	7.68	6.27	64.52	7.77	6.44
EtOH	VIb	76—78	44	$C_{14}H_{21}O_3N$	66.90	8.42	5.57	66.64	8.60	5.81
	VIIb	—	—a)							
n-PrOH	VIc	149—150.5	28	$C_{22}H_{28}O_{10}N_4$ b)	51.96	5.55	11.02	52.12	5.86	11.30
	VIIc	87—88	6	$C_{14}H_{21}O_3N$	66.90	8.42	5.57	66.96	8.14	5.42
CH_2=$CHCH_2OH$	VId	60.5—61	20	$C_{16}H_{21}O_3N$	69.79	7.69	5.09	69.48	7.67	5.00
	VIId	84—85	2	$C_{20}H_{22}O_{10}N_4$ b)	50.21	4.64	11.71	50.19	4.44	11.76
$C_6H_5CH_2OH$	VIe	123—123.5	6	$C_{24}H_{25}O_3N$	76.77	6.71	3.71	76.91	6.73	3.81
	VIIe	119—120	7	$C_{18}H_{21}O_3N$	72.21	7.07	4.68	72.60	7.19	4.46
$C_6H_5CH_2CH_2OH$	VIf	126.5—127	12	$C_{26}H_{29}O_3N$	77.39	7.24	3.47	77.63	7.28	3.53
	VIIf	130.5—131.5	13	$C_{19}H_{23}O_3N$	72.82	7.40	4.47	72.77	7.47	4.53
iso-PrOH	VIg	193—194	6	$C_{22}H_{28}O_{10}N_4$ b)	51.96	5.55	11.02	51.68	5.72	10.94
	VIIg	—	—a)							
p-$MeOC_6H_4CH_2OH$	VIh	169—170.5	4	$C_{26}H_{29}O_5N$	71.70	6.71	3.22	71.82	6.75	3.32
	VIIh	107—108	9	$C_{19}H_{23}O_4N$	69.28	7.04	4.25	69.29	7.12	4.08

a) Formation of the products was observed by means of NMR spectrum.
b) picrate

The assumption was shown to be correct by the result that the product ratio in the case of benzyl or β-phenethyl alcohol was below 1.

As described above, reaction in alcohols including BF_3-etherate was found to give the corresponding 6,10-dialkoxy and 10-monoalkoxy derivatives (except in the case of MeOH) without changing the dienone moiety. Therefore, in order to clarify whether the reaction took place or not in the presence of conc. H_2SO_4 instead of BF_3-etherate, similar treatment with alcohols containing conc. H_2SO_4 were performed. The result was given in Table II.

Table II. Yield of VI and VII (in the Presence of conc. H_2SO_4)

Solvent	Compound	Yield (%)
MeOH	VIa (=VIIa)	15
EtOH	VIb	22
	VIIb	—a)
n-PrOH	VIc	19
	VIIc	5

a) Formation of VIIb was observed by means of NMR spectrum.

The experiment showed that alcoholysis of IVa in the presence of conc. H_2SO_4 also proceeded with conserving a dienone part to afford the same products as in that of BF_3-etherate, though yields in the former were lower than those in the latter. Considering the property of conc. H_2SO_4 and BF_3-etherate, however, in the case of conc. H_2SO_4 available alcohols would be limited because of their unfavorable reaction or dehydration. For instance reaction in benzyl alcohol was unsuccessful.

Now that the reaction pathway was considered, it would be necessary first of all to solve whether alkyl cation or alcohol itself was concerned with the reaction as attacking entity. Therefore, *p*-methoxybenzyl alcohol was chosen. Since *p*-methoxybenzyl alcohol in the presence of BF_3-etherate would more easily result in the corresponding benzyl cation than benzyl alcohol, the product in the former would be formed in much higher yield than that in the latter, provided that the reaction with alkyl cation took place.

With this in mind, reaction of IVa with *p*-methoxybenzyl alcohol including BF_3-etherate was carried out to furnish the corresponding 6-*p*-methoxybenzyloxy- and 6-methoxy-10-*p*-methoxybenzyloxy compound [(VIg) and (VIIg)] in 4% and 9% yield, respectively (Table I). The above product yield (13%) was parallel to that (13%) in the case of benzyl alcohol. Thus 10-acetoxy and 6-methoxy group were proved to react not with alkyl cation but alcohol itself.

On the basis of the above result, the reaction pathway would be inferable as pictured in Chart 2. The reaction would be started with polarization of 7-carbonyl group in acidic medium. Following the step, 1,2-migration of acetoxy group at 10- to 9- position and successive concerted addition of alcohols to 6-position by a $S_N 2'$ type reaction would give an intermediate (VIII). Another intermediate (IX) appeared to be formed by attack of alcohol to 10-position (by a $S_N 2'$ type reaction).

VIII and IX were perhaps in a state of equilibrium because of allylic type rearrangement of alkoxy group. Thus elimination of acetic acid from IX would give rise to VII. However, considering the steric effect due to alkyl chain, the possibility of IX as an intermediate would be negligible. Thereupon, an intermediate (VIII)[7] would be prefered. Detouch of MeOH from VIII would be accompanied by a $S_N 2'$ type addition of alcohols to 10-position giving X, while elimination of acetic acid would give rise to XI. Furthermore, 6,10-dialkoxy product (VI) would be formed by elimination of acetic acid from the former. 10-Mono-alkoxy product (VII) was assumably formed by detouch followed by a $S_N 2'$ type addition of alcohols to 10-position.

At the mention of the product ratio, it could be explained as follows. Namely, if alkyl chain in alcohols were not so bulky (in the case of MeOH, EtOH, *n*-PrOH, or $CH_2=CHCH_2OH$), the reaction leading to VI through X would be favored. For alcohols would approach to 10-position from the opposite side to 9-acetoxy group because of its steric hindrance, so that detouch of methanol (by a $S_N 2'$ type reaction) took place probably. If alkyl chain were more bulky (in the case of $C_6H_5CH_2OH$, $C_6H_5CH_2CH_2OH$, *p*-$MeOC_6H_4CH_2OH$, or iso-PrOH), however, the reaction would be initiated with elimination of acetic acid affording XI, since direct attack of alcohols on 10-position appeared to be somewhat prevented by the steric hindrance due to both 6-alkoxy and 9-acetoxy group. Accordingly, a $S_N 2'$ type addition of alcohols to 10-position from the opposite side to 6-alkoxy group would proceed predominantly giving VII.

It has been found in general that rearrangements of *p*-quinols[3,4] or *p*-quinol ethers[8] normally proceed in migration of alkyl groups, although rearrangements of *p*-quinol acetates[3,4,8] proceed in migration of acetoxy groups. However, acid-catalysed treatment (Ac_2O–

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7) Possible existence of VIII as an intermediate would be supported by the result that only prolonged treatment (13 hr) of *p*-quinol (XIII)[1] in EtOH containing BF_3-etherate gave VIb.

8) E. Hecker and E. Meyer, *Chem. Ber.*, **97**, 1926 (1967).

conc. H_2SO_4) of IVa or *p*-quinol (XII) has been shown to give only 4,7-diacetate (Va). This suggested that the same treatment of *p*-quinol ethers (VI or VII) as noted in IVa would result in the corresponding 4,7-diacetate (XIII or Va). Then reaction of VIa with Ac_2O containing conc. H_2SO_4 was carried out to give only Va as expected. Similarly, the reaction of VIb gave rise to the corresponding 4,7-diacetate (XIII) whose structure was confirmed by means of its NMR spectrum and elemental analysis. The above result was in striking contrast to the earlier observation,[3,4,8] taking account of the fact that the same product was obtained regardless of substituents at 10-position in starting material.

In conclusion, acid-catalysed alcoholysis of *p*-quinol acetate (IVa) in various alcohols was proved to afford the corresponding 6,10-dialkoxy and 10-monoalkoxy product (VI and VII), in which the product ratio was depndent on length of alkyl chain in alcohols used. Thus the present reaction would be regarded as the first instance on stereochemically controlled allylic addition in a compound (IVa).

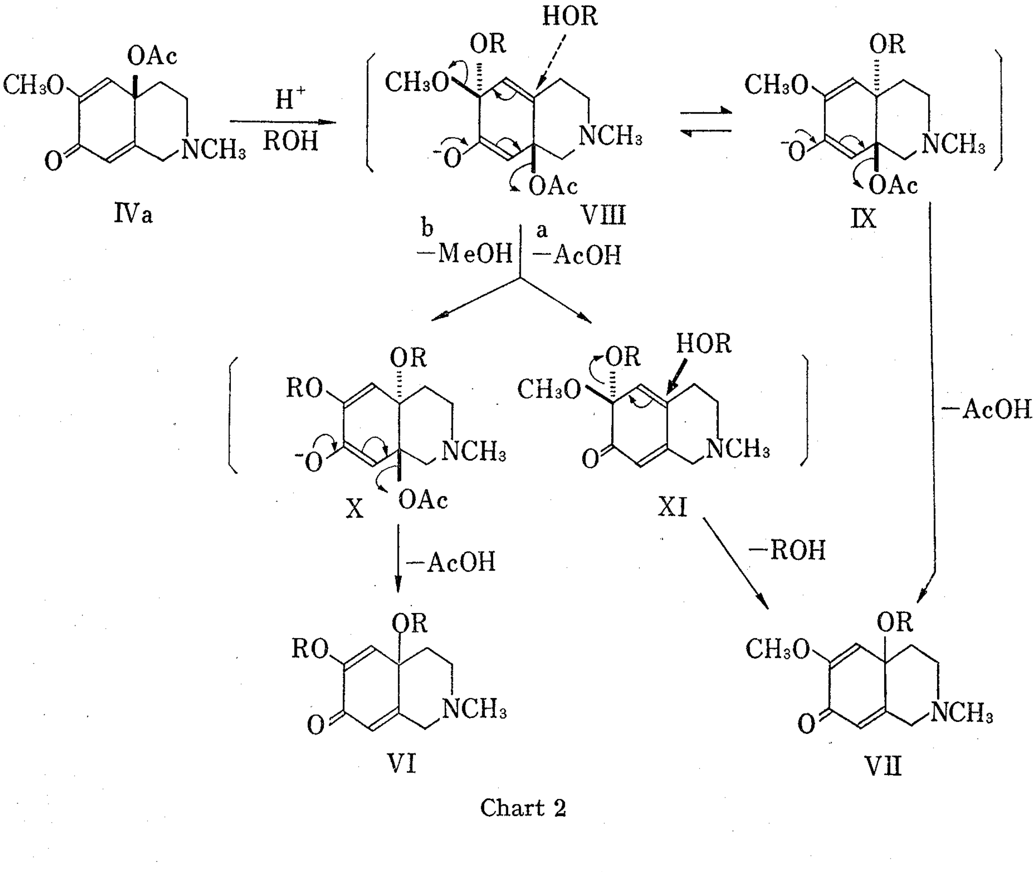

Chart 2

Experimental[9]

General Procedure for Reaction of IVa with Alcohols in the Presence of BF_3-etherate——To an ice-cooled, stirred solution of IVa in alcohols, BF_3-etherate was dropwise added and the whole was stirred at room temperature. After removal of the solvent (in the case of MeOH, EtOH, $CH_2=CHCH_2OH$ or *n*-PrOH) under reduced pressure H_2O was added to the residue or after addition of H_2O to the reaction mixture (in the case of $C_6H_5CH_2OH$, $C_6H_5CH_2CH_2OH$ or *p*-$MeOC_6H_4CH_2OH$) the solvent was washed with ether. The aqueous

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[9] All melting points were measured on a Yanagimoto micro melting point measuring apparatus and uncorrected. NMR spectra were taken with Japan Electron Optics Lab. Model JNM-4H-100 spectrometer in $CDCl_3$ (5—10% solution) using $(CH_3)_4Si$ as internal standard. Following abbreviations were used: s, singlet; bs, broad singlet; d, doublet; t, triplet; q, quartet; AB_q, AB quartet; m, multiplet. IR spectra were measured with a Hitachi EPI-S_2 spectrometer. The organic layer was dried over $MgSO_4$ and column chromatography was run on silicic acid (Mallinckrodt).

solution was basified with K_2CO_3 (powder) and the product was taken up in $CHCl_3$. The $CHCl_3$ layer was washed with brine and dried. Evaporation of the solvent gave an oil which was chromatographed.

(1) MeOH: IVa (1.17 g), MeOH (8 ml) and BF_3-etherate (1.5 g) were used. The mixture was stirred for 0.5 hr. Chromatography of an oil (769 mg) was carried out. Elution with $CHCl_3$–MeOH (100:1) afforded a solid (VIa) (411 mg, 40%), mp 105—108°, which was recrystallized from *n*-hexane to colorless prisms of VIa, mp 112—113°. NMR τ: 7.60 (3H, s, NCH_3), 7.00, 6.73 (2H, AB_q, $J=12.5$ Hz, C-1 H_2), 6.95 (3H, s, C-10 OCH_3), 6.26 (3H, s, C-6 OCH_3), 4.44, 3.68 (each 1H, s, C-8 and C-5 H). IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1670, 1655, 1630 (dienone).

(2) EtOH: IVa (1.7 g), EtOH (10 ml) and BF_3-etherate (3.06 g) were used. The mixture was stirred for 0.5 hr. Chromatography of an oil (1.67 g) was performed. Elution with CH_2Cl_2–MeOH (100:1) furnished a solid (VIb) (882 mg, 44%), mp 75—80°, which was recrystallized from *n*-hexane to colorless prisms of VIb, mp 76—78°. NMR τ: 8.84, 8.56 (each 3H, t, $J=7.0$ Hz, C-10 and C-6 $OCH_2C\underline{H}_3$), 7.61 (3H, s, NCH_3), 7.05—6.62 (4H, m, C-1 H_2 and C-10 $OC\underline{H}_2CH_3$), 6.09 (2H, q, $J=7.0$ Hz, C-6 $OC\underline{H}_2CH_3$), 4.39, 3.70 (each 1H, s, C-8 and C-5). IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1680, 1655, 1630 (dienone). NMR spectrum of the crude product showed a singlet at τ 6.27 (C-6 OCH_3) and a quartet at τ 6.09 ($J=7.0$ Hz, C-6 $OC\underline{H}_2CH_3$). IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1675, 1655, 1630 (dienone).

(3) *n*-PrOH: IVa (1.7 g), *n*-PrOH (10 ml) and BF_3-etherate (3.1 g) were used. On addition of BF_3-etherate to a solution of IVa in *n*-PrOH (an oil separated initially disappeared soon) the whole was stirred for 1 hr. An oil (1.95 g) was chromatographed. Elution with CH_2Cl_2–MeOH (100:1)—(100:2) gave an oil (VIc) (559 mg, 28%); picrate, mp 149—150.5° (iso-PrOH). Free base. NMR τ: 9.09, 8.98 (each 3H, t, $J=7.5$ Hz, C-10 and C-6 $OCH_2CH_2C\underline{H}_3$), 7.60 (3H, s, NCH_3), 6.23 (2H, t, $J=7.5$ Hz, C-6 $OC\underline{H}_2CH_2CH_3$), 4.42, 3.70 (each 1H, s, C-8 and C-5 H). Picrate. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1685, 1660, 1630 (dienone). Successive elution with CH_2Cl_2–MeOH (100:2) afforded an oil (144 mg) whose treatment with *n*-hexane furnished a solid (VIIc) (107 mg, 6%), mp 85—87°. Recrystallization from *n*-hexane gave colorless prisms of VIIc, mp 87—88°. NMR τ: 9.08 (3H, t, $J=7.5$ Hz, C-10 $OCH_2CH_2C\underline{H}_3$), 7.59 (3H, s, NCH_3), 6.27 (3H, s, C-6 OCH_3), 4.38, 3.70 (each 1H, s, C-8 and C-5 H).

(4) $CH_2{=}CHCH_2OH$: IVa (1.85 g), $CH_2{=}CHCH_2OH$ (10 ml) and BF_3-etherate (3.3 g) were used. The mixture was stirred for 0.5 hr. Chromatography of an oil (1.76 g) was started with C_6H_6–CH_2Cl_2 (1:1). Elution with CH_2Cl_2–MeOH (100:2) gave a solid (VId) (415 mg, 20%), mp 57.5—59°, which was recrystallized from *n*-hexane to colorless prisms of VId, mp 59—60.5°. NMR τ: 7.60 (3H, s, NCH_3), 6.96, 6.73 (2H, AB_q, $J=12.5$ Hz, C-1 H_2), 6.50—6.20 (2H, m, C-10 $OC\underline{H}_2CH{=}CH_2$), 5.55 (2H, d, $J=5$ Hz, C-6 $OC\underline{H}_2CH{=}CH_2$), 4.90—4.50 (4H, m, C-6 and C-10 $OCH_2CH{=}C\underline{H}_2$), 4.30—3.90 (2H, m, C-6 and C-10 $OCH_2C\underline{H}{=}CH_2$), 4.37, 3.69 (each 1H, s, C-8 and C-5 H). IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1675, 1650, 1625 (dienone). Subsequently, elution with CH_2Cl_2–MeOH (100:3) afforded an oil (VIId) (33 mg, 2%); picrate, mp 84—85° (iso-PrOH). Free base. NMR τ: 7.60 (3H, s, NCH_3), 6.97, 6.73 (2H, AB_d, C-1 H_2), 6.27 (3H, s, C-6 OCH_3), 4.90—4.50 (2H, m, C-10 $OCH_2CH{=}C\underline{H}_2$), 4.27—3.90 (1H, m, C-10 $OCH_2C\underline{H}{=}CH_2$), 4.36, 3.69 (each 1H, s, C-8 and C-5 H). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1675, 1650, 1630 (dienone).

(5) $C_6H_5CH_2OH$: IVa (1.8 g), $C_6H_5CH_2OH$ (10 ml) and BF_3-etherate (3.06 g) were used. The mixture was stirred for 0.5 hr. Chromatography of an oil (1.02 g) was started with C_6H_6–CH_2Cl_2 (1:1). Elution with CH_2Cl_2–MeOH (100:1.5) furnished a solid (VIe) (149 mg, 6%), mp 113—119°, which was recrystallized from *n*-hexane to colorless needles of VIe, mp 123—123.5°. NMR τ:7.58 (3H, s, NCH_3), 6.92, 6.70 (2H, AB_q, $J=12.5$ Hz, C-1 H_2), 5.98 (2H, s, C-10 $OC\underline{H}_2C_6H_5$), 5.13, 4.93 (2H, AB_q, $J=12.5$ Hz, C-6 $OC\underline{H}_2C_6H_5$), 4.33, 3.62 (each 1H, s, C-8 and C-5 H), 2.95—2.55 (10H, m, C-6 and C-10 $OCH_2C_6\underline{H}_5$). IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1675, 1650, 1625 (dienone).

Successively, elution with CH_2Cl_2–MeOH (100:2) furnished a solid (VIIe) (150 mg, 7%), mp 119—120°, which was recrystallized from *n*-hexane to colorless prisms of VIIe, mp 149—151°. NMR τ: 7.58 (3H, s, NCH_3), 6.89, 6.69 (2H, AB_q, $J=12.5$ Hz, C-1 H_2), 6.33 (3H, s, C-6 $OC\underline{H}_3$), 5.83, 5.69 (2H, ABq, $J=12.5$ Hz, C-10 $OC\underline{H}_2C_6H_5$), 4.38, 3.62 (each 1H, s, C-8 and C-5 H), 2.65 (5H, s, C-10 $OCH_2C_6\underline{H}_5$). IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1670, 1645, 1620 (dienone).

(6) iso-PrOH: IVa (1.7 g), iso-PrOH (10 ml) and BF_3-etherate (3.3 g) were used. The mixture was stirred for 12 hr. Chromatography of an oil (1.18 g) was carried out. Elution with CH_2Cl_2–MeOH (100:1.5) furnished an oil (VIf) (116 mg, 6%); picrate, mp 193—194° (iso-PrOH). Free base. NMR τ: 8.90, 8.66 [each 6H, d, $J=6.3$ Hz, C-10 and C-6 $OCH(C\underline{H}_3)_2$], 7.61 (3H, s, NCH_3), 6.51, 5.61 [each 1H, quintet, $J=6.3$ Hz, C-10 and C-6 $OC\underline{H}(CH_3)_2$], 4.33, 3.74 (each 1H, s, C-8 and C-5 H). Successively, elution with CH_2Cl_2–MeOH (100:1.5) gave an oil (160 mg), NMR spectrum of which showed a singlet at τ 6.27 (C-6 OCH_3) and a quintet at τ:5.60 [C-6 $OC\underline{H}(CH_3)_2$]. All efforts to isolate VIIf as pure state were unsuccessful.

(7) $C_6H_5CH_2CH_2OH$: To an ice-cooled, stirred solution of IVa (1.06 g) in $C_6H_5CH_2CH_2OH$ (10 ml), BF_3-etherate (1.8 g) in $C_6H_5CH_2CH_2OH$ (1 ml) was added. The mixture was stirred for 0.5 hr. Chromatography of an oil (818 mg) was undertaken. Elution with CH_2Cl_2–MeOH (100:2) furnished a solid (VIg) (198 mg, 12%), mp 122—124°, which was recrystallized from C_6H_6 to colorless prisms of VIg, mp 126.5—127°. NMR τ: 7.75 (3H, s, NCH_3), 6.70—6.45 (2H, m, C-10 $OC\underline{H}_2CH_2C_6H_5$), 6.20—6.01 (2H, m, C-6 $OC\underline{H}_2CH_2C_6H_5$), 4.58, 3.76 (each 1H, s, C-8 and C-5 H), 1.85—1.60 (10H, m, C-6 and C-10 $OCH_2CH_2C_6\underline{H}_5$). IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1670, 1650, 1625 (dienone). Successively, elution with CH_2Cl_2–MeOH (100:2) afforded a

solid (VIIg) (169 mg, 13%), mp 110—120°, which was recrystallized from *n*-hexane to colorless needles of VIIg, mp 130.5—131.5°. NMR τ: 7.74 (3H, s, NCH_3), 6.60—6.48 (2H, m, C-10 $OC\underline{H}_2CH_2C_6H_5$), 6.36 (3H, s, C-6 OCH_3), 4.53, 3.75 (each 1H, s, C-8 and C-5 H), 1.84—1.65 (5H, m, C-10 $OCH_2CH_2C_6\underline{H}_5$). IR ν_{max}^{KBr} cm^{-1}: 1675, 1650, 1630 (dienone).

(8) *p*-$MeOC_6H_5CH_2OH$: To an ice-cooled, stirred solution of IVa (1.8 g) in *p*-$MeOC_6H_4CH_2OH$ (10 ml), BF_3-etherate (3.8 g) in anhydrous THF (7 ml) was added. The mixture was stirred for 1 hr. Chromatography of an oil (1.64 g) was started with C_6H_6–CH_2Cl_2 (1:1). Elution with CH_2Cl_2–MeOH (100:1.5) yielded a solid (VIh) (136 mg, 4%), mp 166—167.5°, which was recrystallized from C_6H_6 to colorless prisms of VIh, mp 169—170.5°. NMR τ: 7.60 (3H, s, NCH_3), 6.92, 6.72 (2H, ABq, $J=12$ Hz, C-1 H_2), 6.21, 6.19 (each 3H, s, C-10 and C-6 $OCH_2C_6H_4OC\underline{H}_3$), 6.06 (2H, bs, C-10 $OC\underline{H}_2C_6H_4OCH_3$), 5.19, 4.97 (2H, ABq, $J=12.5$ Hz, C-6 $OC\underline{H}_2C_6H_4OCH_3$), 4.35, 3.65 (each 1H, s, C-8 and C-5), 2.18—1.62 (8H, m, C-6H and C-10 $OCH_2C_6\underline{H}_3OCH_3$). Subsequently, elution with CH_2Cl_2–MeOH (100:1.5) furnished a solid (VIIh) (199 mg, 9%), mp 84—94°, which was recrystallized from *n*-hexane to colorless fine needles of VIIh, mp 107—108°. NMR τ: 7.60 (3H, s, NCH_3), 6.91, 6.70 (2H, AB_q, $J=12.5$ Hz, C-1 H_2), 6.33, 6.19 (each 3H, s, C-6 OCH_3 and C-10 $OCH_2C_6H_4OC\underline{H}_3$), 5.92, 5.78 (2H, AB_q, $J=10.1$ Hz, C-10 $OC\underline{H}_2C_6H_4OCH_3$), 4.39, 3.65 (each 1H, s, C-8 and C-5 H), 3.11, 2.78 (4H, AB_q, $J=7.5$ Hz, C-10 $OCH_2C_6\underline{H}_4OCH_3$).

General Procedure for Reaction with Alcohols in the Presence of conc. H_2SO_4——To an ice-cooled, stirred solution of IVa in alcohols, an alcoholic solution of conc. H_2SO_4 was added. The whole was stirred for 1 hr at room temperature. The same treatment as noted above (in the case of MeOH) afforded an oil which was chromatographed.

(1) MeOH: IVa (226 mg), MeOH (4 ml) and a methanolic solution of conc. H_2SO_4 [conc. H_2SO_4 (170 mg) and MeOH (4 ml)] were used. Chromatography of an oil (159 mg) was performed. Elution with CH_2Cl_2–MeOH (100:1) yielded an oil (52 mg), whose treatment with *n*-hexane gave VIa (32 mg, 15%), mp 111—112°. This was identical with a product obtained in the case of MeOH (BF_3-etherate) in all respects.

(2) EtOH: IVa (852 mg), EtOH (7 ml) and an ethanolic solution of conc. H_2SO_4 [conc. H_2SO_4 (650 mg) and EtOH (3 ml)] were used. Chromatography of an oil (573 mg) was carried out. Elution with CH_2Cl_2–MeOH (100:1) furnished an oil (332 mg) which was treated with *n*-hexane to give VIb (186 mg, 22%) mp 78—79.5°. This was identical with a product obtained in the case of EtOH (BF_3-etherate) in all respects. NMR spectrum of the product obtained on removal of the solvent showed a singlet at τ 6.27 (C-6 OCH_3).

(3) *n*-PrOH: IVa (1.6 g), *n*-PrOH (10 ml) and a *n*-propanolic solution of conc. H_2SO_4 [conc. H_2SO_4 (1.3 g) and *n*-PrOH (6 ml)] were used. Chromatography of an oil (1.5 g) was undertaken. Elution with $CHCl_3$–MeOH (200:1) afforded an oil (VIe) (333 mg, 19%); picrate, mp 149.5—150.5° (iso-PrOH). This was identical with a product obtained in the case of *n*-PrOH (BF_3-etherate) by the comparison of IR spectrum and by mixed fusion. Successively, elution with $CHCl_3$–MeOH (200:1)—(100:1) yielded an oil (204 mg), whose treatment with *n*-hexane gave VIIc (87 mg, 5%), mp 87—88°. This was identical with a product obtained in the case of *n*-PrOH (BF_3-etherate) by the comparison of IR spectrum and by mixed fusion.

Reaction of VI in Acetic Anhydride containing conc. H_2SO_4——The same treatment of VI as described previously1) was carried out for 0.5 hr.

(1) Va: VIa (20 mg), Ac_2O (0.2 ml) and a solution of conc. H_2SO_4 (20 mg) in Ac_2O (0.3 ml) were used. Usual work-up of the reaction mixture gave Va (19 mg, 77%), mp 80—82° (*n*-hexane), which was identical with an authentic specimen1) by comparison of IR spectrum and by mixed fusion.

(2) XIV: VIb (90 mg), Ac_2O (1 ml) and a solution of conc. H_2SO_4 (120 mg) in Ac_2O (1 ml) were used. An oil (112 mg) obtained on usual work-up of the reaction mixture was chromatographed. Elution with CH_2Cl_2–MeOH (100:1) gave a solid (XIV) (55 mg, 50%), mp 73—75°, which was recrystallized from petroleum ether (bp 33—35°) to colorless prisms of XIV, mp 76—76.5°. *Anal.* Calcd. for $C_{16}H_{21}O_5N$: C, 62.52; H, 6.88; N, 4.56. Found: C, 62.14; H, 7.07; N, 4.54. NMR τ: 8.62 (3H, t, $J=7.5$ Hz, C-6 $OCH_2C\underline{H}_3$), 7.86, 7.69 (each 3H, s, OAc × 2), 7.52 (3H, s, NCH_3), 6.70, 6.20 (2H, AB_q, $J=15$ Hz, C-1 H_2), 5.94 (2H, q, $J=7.5$ Hz, C-6 $OC\underline{H}_2CH_3$), 4.02 (1H, t, $J=2.5$ Hz, C-4 H), 3.19, 3.02 (each 1H, s, aromatic ring proton). IR ν_{max}^{KBr} cm^{-1}: 1770 (C-6 OAc), 1730 (C-4 OAc), 1620 (C=C).

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