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# FACILE ACETYLATION OF A TERTIARY HYDROXYL GROUP AND AN UNUSUAL DESHIELDING PHENOMENON BY AN ACETOXYL GROUP IN NMR SPECTRA

K. YAMADA, S. TAKADA, S. NAKAMURA and Y. HIRATA

Chemical Institute, Faculty of Science, Nagoya University, Chikusa, Nagoya, Japan

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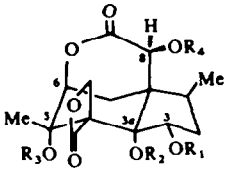
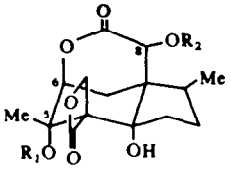
**Abstract**—Facile acetylation of a tertiary OH group was found to occur under mild conditions in derivatives of anisatin (I) and neoanisatin (VI), toxic compounds obtained from *Illicium Anisatum* L. Thus, noranisatin (VIII) and norneoanisatin (XV) gave the diacetate Xa and the monoacetate XVI, respectively. The structural feature of facile acetylation of a tertiary OH group is discussed. An abnormal deshielding effect to a methine proton by a neighbouring acetoxyl group was observed in the NMR spectra. In XV, acetylation of the tertiary OH group on C-5 caused a downfield shift of the C-6 proton by 1·1 ppm. The same phenomenon was observed in compounds II, VIII and XI.

## INTRODUCTION

RECENTLY, the structures of anisatin (I) and neoanisatin (VI), toxic compounds isolated from *Illicium Anisatum* L were established.[1] In the course of the structure elucidation of these compounds, we encountered some puzzling phenomena on acetylation and the NMR spectra of the acetylated products, which brought confusion in the early stage of our structural studies. In this paper, the unusual phenomena on acetylation and the NMR spectra will be clarified and discussed.





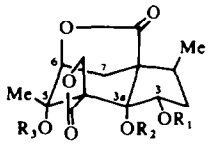
I: $R_1 = R_2 = R_3 = R_4 = H$
II: $R_1 = Ac$; $R_2 = R_3 = R_4 = H$
III: $R_1 = R_3 = R_4 = Ac$; $R_2 = H$
IV: $R_1, R_2 =$ >CO; $R_3 = R_4 = H$
V: $R_1, R_2 =$ >CO; $R_3 = H$; $R_4 = Ac$

VI: $R_1 = R_2 = H$
VII: $R_1 = R_2 = Ac$

*Facile acetylation of a tertiary hydroxyl group*

On treatment with acetic anhydride (one molar equiv) in pyridine at room temp overnight, noranisatin (VIII)[1a, 1e] gives noranisatin monoacetate (IX),[1a, 1e] whereas VIII affords noranisatin diacetate (Xa), $C_{18}H_{22}O_9$ on standing with excess acetic anhydride in pyridine at room temperature for six days. On heating noranisatin (VIII) with

acetic anhydride and pyridine for several hours, only the diacetate Xa is obtained, indicating that further acetylation of the diacetate Xa does not occur. Since noranisatin diacetate contains one OH and two acetoxyl groups, two structures Xa and Xb are conceivable for this compound.



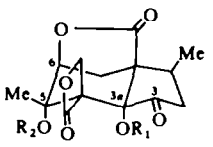
VIII: $R_1 = R_2 = R_3 = H$
IX: $R_1 = Ac$; $R_2 = R_3 = H$
Xa: $R_1 = R_3 = Ac$; $R_2 = H$
Xb: $R_1 = R_2 = Ac$; $R_3 = H$



XI: $R_1, R_2 =$ CO; $R_3 = H$

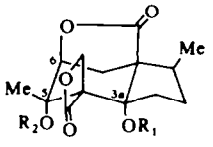


XII: $R_1, R_2 =$ CO; $R_3 = Ac$



XIII: $R_1 = R_2 = H$
XIVa: $R_1 = H$; $R_2 = Ac$
XIVb: $R_1 = Ac$; $R_2 = H$

One might rationalize the facile formation of noranisatin diacetate by assuming that the secondary OH group of VIII is acetylated first and the resulting acetoxyl then migrates either to the tertiary OH on C-3a or to the one on C-5 via the C-3a OH. This explanation is untenable due to the ready acetylation of norneoanisatin (XV) lacking in a secondary OH on C-3 (*vide infra*). Acetylation of noranisatinone (XIII)[1a, 1e] under forcing conditions affords noranisatinone monoacetate (XIV) $C_{16}H_{18}O_8$, which must be represented by one of the two alternative structures, XIVa and XIVb. From the NMR spectral evidence described later, the structures of noranisatin diacetate and noranisatinone monoacetate are Xa and XIVa, respectively. Norneoanisatin (XV)[1d, 1e] is also acetylated under the following mild conditions, although it contains no secondary OH group. Norneoanisatin monoacetate (XVI) $C_{16}H_{20}O_7$ is obtained on treatment of XV with excess acetic anhydride and pyridine at room temperature for six days. The NMR spectrum of XVI shows that acetylation occurs at the C-5 OH group, the details of which will be discussed later.



XV: $R_1 = R_2 = H$
XVI: $R_1 = H$; $R_2 = Ac$

In marked contrast to the compounds mentioned above, noranisatin carbonate (XI)[1a, 1e] is resistant to acetylation. The carbonate XI is recovered unchanged by heating with acetic anhydride–pyridine or by refluxing with acetyl chloride–pyridine in THF. Acetylation of XI to noranisation carbonate acetate (XII) $C_{17}H_{18}O_9$ only is effected by heating with acetic anhydride and *p*-toluenesulphonic acid.

Anisatin (I) containing two secondary OH groups forms a monoacetate, II[1c, 1e] and a triacetate, III.[1c, 1e, 2]

Three acetoxyl groups in the triacetate III must be located at C-3, C-5 and C-8. This inference is confirmed by NMR spectral data (*vide infra*).

Acetylation of the tertiary OH group on C-5 also occurs readily in neoanisatin (VI) on treatment with acetic anhydride and pyridine at ca. 40°, to give a diacetate VII.[1d, 1e] Anisatin carbonate (IV)[1c] with acetic anhydride and pyridine affords anisatin carbonate acetate (V) $C_{18}H_{20}O_{10}$. In this case, acetylation of the tertiary OH group on C-5 does not occur, as in the attempted acetylation of the corresponding nor-carbonate XI, under the mild conditions.

As described above, acetylation of a tertiary OH group takes place in anisatin, neoanisatin and their derivatives under mild conditions (i.e. with acetic anhydride–pyridine at room temperature or near room temperature). The structural requirement for facile acetylation of a tertiary OH is as follows: two tertiary OH groups disposed in the 1,3-diaxial relationship must be free. In cases where one of the tertiary OH groups is blocked by forming a cyclic carbonate, facile acetylation of the other tertiary OH does not occur.

*Unusual deshielding effect to a methine proton by a neighbouring acetoxyl group*

It is a well known phenomenon in the NMR spectra that a methine proton on carbon bearing a OH group exhibits a characteristic shift of ca. 1·1 ppm to lower field on acetylation of the OH group.[3] This effect is widely employed as a convenient and reliable method for the detection of secondary OH groups.

However, in the derivatives of anisatin (I) and neoanisatin (VI), it was found that a methine proton similarly undergoes a downfield shift by ca. 1 ppm on acetylation of a vicinal tertiary OH group.[4] The NMR spectra of noranisatin carbonate (XI) and its acetate XII indicate that the signal of the C-6 proton in XI moves to lower field by 0·89 ppm by acetylation of the tertiary OH group, as illustrated in the Table. A downfield shift of the signal due to the C-6 proton is evidently caused by acetylation of the tertiary OH group on C-5.

In the NMR spectra of noranisatin (VIII) and its monoacetate IX, the signal of the C-3 proton moves to lower field (from 4·60 ppm to 5·65 ppm) by acetylation of the secondary OH as expected, while the signal of the C-6 proton remains essentially unchanged (4·31 ppm in VIII and 4·37 ppm in IX). On the other hand, the NMR spectra of noranisatin (VIII) and its diacetate Xa show that acetylation in this case causes a respective downfield shift of both signals due to the C-3 and C-6 methine protons by ca. 1 ppm (Fig. 1). The NMR spectra of the acetates II and III of anisatin (I) also exhibit the unusual deshielding effect to the C-6 methine by the C-5 acetoxyl group, as illustrated in the Table. As described above, this phenomenon was observed in noranisatin carbonate (XI) and its acetate XII, in which case the only available position for acetylation is the tertiary OH on C-5. On the basis of this finding it was deduced that, of the two tertiary OH groups, facile acetylation occurs at the one on C-5 in the derivatives of anisatin, since they reveal this effect in the NMR spectra.

The same effect was observed in the NMR spectra of norneoanisatin (XV) and its acetate XVI (Fig. 2 and Table).

The anisotropic effect of a tertiary acetoxyl group accounts for the unusual deshielding phenomenon mentioned above. The structural feature of compounds exhibiting this phenomenon is that an equatorial proton deshielding by acetylation is vicinal to the axial tertiary OH, to which another tertiary OH function is disposed

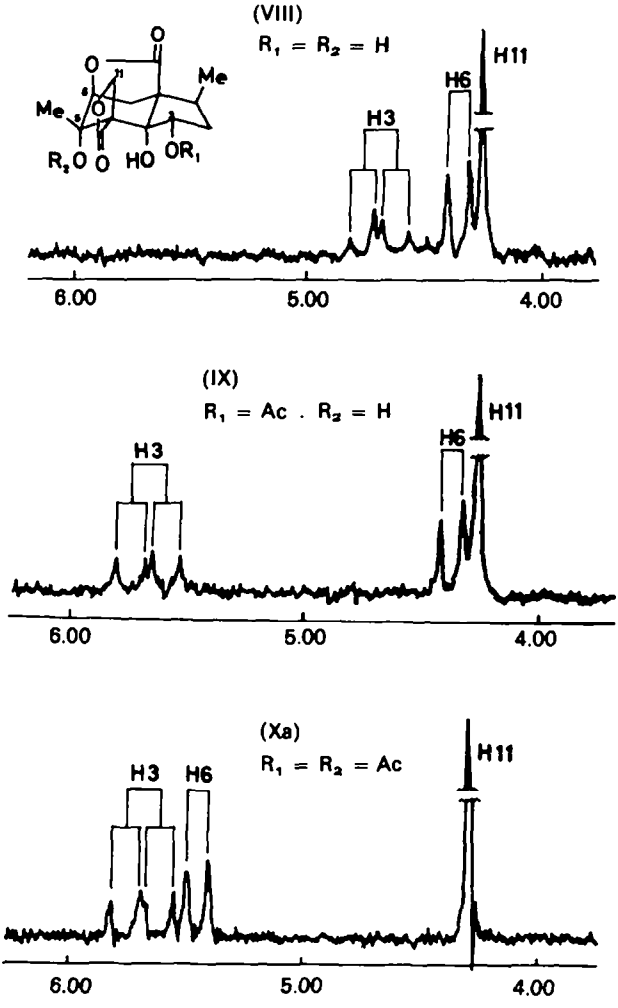



FIG. 1 The NMR spectra of noranisatin (VIII), the monoacetate (IX) and the diacetate (Xa): ppm from internal TMS at 60 Mc in deuteriochloroform.

TABLE 1. THE EFFECT OF ACETYLATION OF THE C-5 HYDROXYL GROUP ON CHEMICAL SHIFT OF THE C-6 PROTON

| Compound | Chemical shift* of C-6 proton | Shift value (ppm) |
|---|---|---|
| II | 4·50 (m) | 1·16 |
| III | 5·66 (q) | |
| VIII | 4·31 (d) | 1·12 |
| Xa | 5·43 (d) | |
| XI | 4·59 (d) | 0·89 |
| XII | 5·48 (q) | |
| XV | 4·28 (d) | 1·11 |
| XVI | 5·39 (q) | |

* ppm from TMS in deuterioacetone (XI, XII) and deuteriochloroform (all other compounds); d, doublet; q, quartet; m, multiplet.

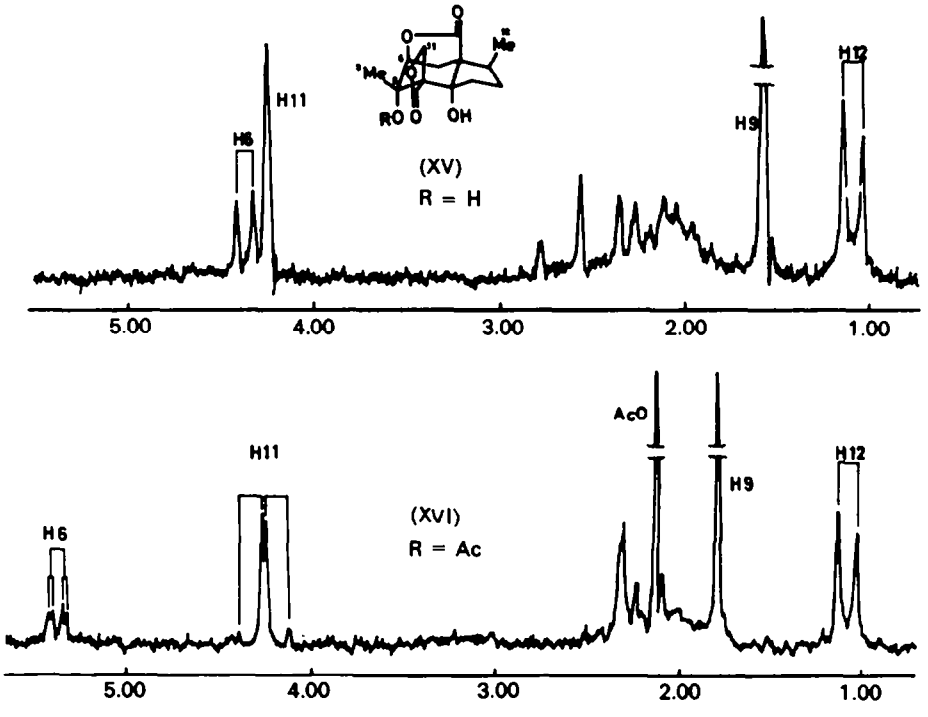
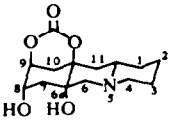



FIG. 2 The NMR spectra of norneoanisatin (XV) and the monoacetate (XVI): ppm from internal TMS at 60 Mc in deuteriochloroform (after hydrogen-deuterium exchange).

in a 1,3-diaxial relationship. Kupchan *et al.* studied acetylation of compounds structurally similar to those in the present paper and reported interesting results.[5] For example, they observed that on acetylation of the tertiary OH group on C-6a in XVII, the signal of an equatorial proton on C-6 moves to lower field by 0·9 ppm.



XVII

## EXPERIMENTAL

All m.ps were uncorrected. The IR spectra were recorded with a JASCO IR-S spectrometer and with a JASCO DS-402G spectrometer. The NMR spectra were recorded with Varian Associates spectrometer, A-60; only prominent peaks are cited; the chemical shifts are given in ppm relative to internal TMS; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; coupling constants are given in c/s. TLC analysis was performed on silica gel G or silica gel GF (E. Merck, A.G. Germany). For column chromatography, Mallinckrodt silicic acid (100 mesh, Mallinckrodt, U.S.A.) was used.

*Noranisatin diacetate* (Xa)

A soln of VIII (27 mg) in $Ac_2O$ (0·2 ml) and pyridine (0·5 ml) was kept at room temp for 6 days. Water was added to the soln and the resulting crystals were filtered off. The filtrate was extracted with AcOEt. From the AcOEt extract additional crystals (10 mg) were obtained. Recrystallization from benzene–hexane gave needles of Xa, m.p. ca. 160° (sublimation); IR bands at 1825, 1790, 1745 $cm^{-1}$ (KBr); NMR signals ($CDCl_3$) at 1·10 (3H, d, $J$ = 7·0), 1·80 (3H, s), 2·07 (3H, s), 2·13 (3H, s), 3·50 (1H, s, OH), 4·30 (2H, s), 5·43 (1H, d, $J$ = 5·5, C-6 proton), 5·69 (1H, q, $J$ = 7·5, 9·0, C-3 proton). (Found: C, 56·40; H, 5·83. $C_{18}H_{22}O_9$ requires: C, 56·54; H, 5·80%.)

*Noranisatinone monoacetate* (XIVa)

A soln of XIII (150 mg) in $Ac_2O$ (0·5 ml) and pyridine (2 ml) was kept at room temp for 3 days, warmed at 70° for 1 hr and concentrated under reduced press. Water was added to the residue to give crystals, 134 mg. Recrystallization from $CHCl_3$ gave pure XIVa, m.p. 204–206°; IR bands at 1820, 1785, 1760, 1740 $cm^{-1}$ (KBr). (Found: C, 56·67; H, 5·23. $C_{16}H_{18}O_8$ requires: C, 56·80; H, 5·36%.)

*Norneoanisatin monoacetate* (XVI)

To a soln of XV (50 mg) in pyridine (1 ml) $Ac_2O$ (0·5 ml) was added. The mixture was kept at room temp for 6 days and poured into $H_2O$. The resulting mixture was concentrated under reduced press to give an oily product. TLC analysis showed that the product was a mixture of XV and XVI. The mixture was separated by preparative TLC (developing agent. AcOEt–hexane, 1:1). Crude crystals of XVI (24 mg) obtained by extraction from silica gel G were recrystallized from $CHCl_3$–ether to give pure XVI, m.p. 159–161°; IR bands at 1820, 1775, 1750 $cm^{-1}$ (KBr); NMR spectrum (Fig. 2). (Found: C, 59·34; H, 6·54. $C_{16}H_{20}O_7$ requires: C, 59·25; H, 6.22%.) The starting material, XV (16 mg) was obtained from the mixture by preparative TLC.

*Acetylation of noranisatin carbonate* (XI)

(1) To a soln of XI (135 mg) in THF (3·5 ml) and pyridine (0·1 ml), AcCl (0·1 ml) in THF (1·5 ml) was added. The mixture was kept at room temp for 3 days, refluxed for 1 hr and concentrated under reduced press. Water was added to the residue and the mixture was extracted with two 1·5 ml portions of AcOEt. The AcOEt extracts were washed with $CdCl_2$ aq, sat. $NaHCO_3$ aq and sat. NaCl aq and dried over $Na_2SO_4$. On evaporation of the solvent, crystals (115 mg) were obtained, which were identified as starting material by IR spectral comparison.

(2) A soln of XI (100 mg) in $Ac_2O$ (3 ml)—pyridine (0·1 ml) was kept at room temp for 7 days and heated at ca. 95° for 3 hr. The mixture was concentrated under reduced press. Water was added to the residue and the mixture was extracted with three 4 ml portions of AcOEt. The AcOEt extracts were washed with $CdCl_2$aq, sat. $NaHCO_3$aq and sat. NaClaq and dried over $Na_2SO_4$. On evaporation of the solvent, crystals (82 mg) were obtained and identified as starting material by IR spectral comparison.

(3) A soln of XI (130 mg) and *p*-TsOH (ca. 15 mg) in $Ac_2O$ (5 ml) was kept at room temp for 7 days and heated at ca. 100° for 2 hr. The mixture was concentrated under reduced press to give crude crystals. Water (10 ml) was added and the resulting mixture was extracted with three 10 ml portions of AcOEt. The combined AcOEt extracts were washed with $NaHCO_3$aq, $H_2O$ and sat. NaClaq and dried over $Na_2SO_4$. On evaporation of the solvent, crude crystals (150 mg) were obtained. Recrystallization from $CCl_4$–benzene afforded pure XII, 130 mg, m.p. ca. 200° (sublimation); IR bands at 1850, 1800 (strong), 1750 $cm^{-1}$ (KBr); NMR signals ($CD_3COCD_3$) at 1·15 (3H, d, $J$ = 6·0), 1·86 (3H, s), 2·10 (3H, s), 4·42 (2H, q, AB-type, $J$ = 8·0), 5·48 (1H, q, $J$ = 5·5, 2·0), 5·50 (1H, q, $J$ = 4·5, 2·0). (Found: C, 56·12; H, 5·00. $C_{17}H_{18}O_9$ requires: C, 55·74; H, 4·95%.)

*Anisatin carbonate acetate* (V)

A soln of IV (94 mg) in $Ac_2O$ (1 ml) and pyridine (0·2 ml) was kept at 40° for 30 days and concentrated under reduced press to give a crystalline solid. Recrystallization from $CHCl_3$–acetone gave pure V, 70 mg, m.p. 252–253°; IR bands at 1845, 1815, 1775, 1745 $cm^{-1}$ (KBr). (Found: C, 54·45; H, 5·16. $C_{18}H_{20}O_{10}$ requires: C, 54·54; H, 5·09%.)

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## REFERENCES

[1] [a] K. Yamada, S. Takada, S. Nakamura and Y. Hirata, *Tetrahedron Letters* 4785 (1965); [b] N. Sakabe, Y. Hirata, A. Furusaki, Y. Tomiie and I. Nitta, *Ibid.* 4795 (1965); [c] K. Yamada, S. Takada, S. Nakamura and Y. Hirata, *Ibid.* 4797 (1965); [d] S. Takada, S. Nakamura, K. Yamada and Y. Hirata, *Ibid.* 4739 (1966); [e] K. Yamada, S. Takada, S. Nakamura and Y. Hirata, *Tetrahedron* **24**, 199 (1968).

[2] J. F. Lane, W. T. Koch, N. S. Leeds and G. Gorin, *J. Am. Chem. Soc.* **74**, 3211 (1952).

[3] L. M. Jackman, *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry* p. 55. Pergamon Press. London (1959).

[4] Preliminary communication. S. Takada, K. Yamada, S. Nakamura and Y. Hirata, *Chem. Comm.* 538 (1967).

[5] S. M. Kupchan, J. H. Block and A. C. Isenberg, *J. Am. Chem. Soc.* **89**, 1189 (1967).