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Methyl Signals in the PMR Spectra of Nigakilactones and Nigakihemiacetals

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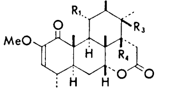
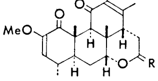
In connection with the structure determination of bitter principles isolated from *Picrasma ailanthoides* Planchon (*P. quassioides* Bennett),[1,2] the PMR spectra of nigakilactones A (I), B (II), C (III), D (IV) (=quassin[3])), E (V), F (VI),[1a,b] H (VII),[1c] J (VIII), K (IX), L (X), M (XI), and N (XII)[1d] were measured. The spectra of nigakihemiacetals A (XIII), B (XIV) (=neoquassin[3])), and C (XV)[1c] were also recorded. The PMR spectra of picrasin B (XVI)[2a](=nigakilactone I[1c]), picrasin D (XVII),[2b,4] picrasin E (XVIII),[2b,4] a monoacetate of nigakilactone J (XIX),[1d] a deacetyl derivative of nigakilactone J (XX),[1d] and dehydroquassin (XXI)[3] were determined as references.

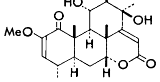
All of these compounds have a quassolidane skeleton (XXII) which possesses four methyl groups at C-4, C-8, C-10, and C-13. We wish to describe an assignment of the methyl signals of these compounds. The result is summarized in Table 1.



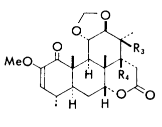
	R₁	R₂	R₃	R₄
(I)	OH	OH	H	H
(II)	OH	OMe	H	H
(III)	OAc	OMe	H	H
(V)	OAc	OMe	OH	H
(VI)	OH	OMe	OH	H
(VII)	OH	OMe	OH	OH
(XI)	OH	OH	H	OH
(XII)	OH	OH	OH	H



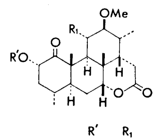
(IV) R = O
(XIV) R = H, OH



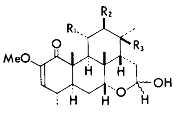
(IX)



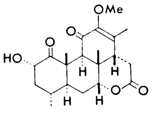
	R₃	R₄
(X)	OH	H
(XVII)	H	H
(XVIII)	H	OH



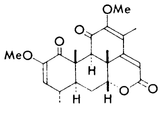
	R′	R₁
(VIII)	H	OAc
(XIX)	Ac	OAc
(XX)	H	OH



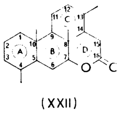
	R₁	R₂	R₃
(XIII)	OH	OMe	OH
(XV)	OH	OH	H
(XXIII)	OAc	OMe	OH



(XVI)



(XXI)



(XXII)

Table 1. PMR spectral data on methyl signals

Compound	4-Me	8-Me	10-Me	13-Me	Compound	4-Me	8-Me	10-Me	13-Me
I	1.10 d ($J=6$)	1.24 s	1.42 s	1.01 d ($J=6.5$)	IV	1.11 d ($J=7$)	1.18 s	1.54 s	1.85 s
II	1.13 d ($J=6.5$)	1.21 s	1.45 s	1.00 d ($J=6.5$)	XIV	1.07 d ($J=6$)	1.05 s	1.49 s	1.83 s
III[e)]	1.10 d ($J=7$)	1.28 s	1.28 s	1.04 d ($J=7$)	XVI	0.93 d ($J=6$)	1.20 s[f)]	1.45 s[f)]	1.91 s
V[e)]	1.08 d ($J=7$)	1.52 s	1.26 s	1.24 s	XXI	1.15 d ($J=6$)	1.27 s	1.53 s	2.00 s
VI	1.11 d ($J=7$)	1.46 s	1.46 s	1.22 s	IX	1.18 d ($J=7$)	1.50 s[d)]	1.45 s[d)]	1.48 s[d)]
VII	1.15 d ($J=7.5$)	1.35 s	1.50 s	1.27 s	X	1.12 d ($J=7$)	1.53 s	1.47 s	1.36 s
XI	1.17 d ($J=6$)	1.20 s	1.50 s	1.10 d ($J=6$)	XVII	1.10 d ($J=7$)	1.28 s	1.43 s	1.10 d ($J=7$)
XII	1.16 d ($J=7$)	1.53 s[b)]	1.50 s[b)]	1.28 s	XVIII	1.10 d ($J=7$)	1.22 s	1.45 s	1.10 d ($J=7$)
VIII	0.90 d ($J=6$)	1.28 s[c)]	1.26 s[c)]	1.04 d ($J=7$)	XIII	1.11 d ($J=7$)	1.34 s	1.44 s	1.20 s
XIX	0.96 d ($J=6$)	1.27 s	1.32 s	1.03 d ($J=7$)	XV	1.13 d ($J=6$)	1.16 s	1.45 s	1.05 d ($J=7$)
XX	0.92 d ($J=6$)	1.22 s	1.40 s	1.04 d ($J=6$)	XXIII	1.03 d ($J=7$)	1.36 s	1.24 s	1.20 s

a) Chemical shifts and coupling constants are expressed in δ value and in Hz, respectively. b, c) Values may be reversed. d) Values may be interchanged. e) These assignments are in accord with those obtained from PMR experiments including NOE.[1b)] f) Reversed values had been described.[8)]

The method utilized for steroids[5)] and triterpenes[6)] was applied to the present investigation,[7)] admitting that the effect caused by a change in a functional group is particularly observed on the signals of methyl groups situated nearly to this functional group, and the effect diminishes rapidly with the distance.

Methyl Group at C-4. A secondary methyl group at C-4 resonates at δ 1.07—1.17 as a doublet for the compounds with a methylated diosphenol moiety in ring A (I—VII, IX—XV, XVII, XVIII, and XXI). A doublet signal of this methyl group appears at δ 0.90—0.96 when ring A is saturated (VIII, XVI, XIX, and XX).

The signal due to the methyl group at C-4 is not practically affected by a structural change in rings C and D.

Methyl Group at C-13. A doublet at δ 1.00—1.10 is observed for a methyl group at C-13 of the compounds with R_3=H (I—III, VIII, XI, XV, and XVII—XX).

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1) a) T. Murae, T. Tsuyuki, T. Ikeda, T. Nishihama, S. Masuda, and T. Takahashi, *Tetrahedron*, **27**, 1545 (1971); b) T. Murae, T. Ikeda, T. Tsuyuki, T. Nishihama, T. Takahashi, and K. Tori, *Tetrahedron Lett.*, **1971**, 3897; c) T. Murae, T. Tsuyuki, T. Ikeda, T. Nishihama, S. Masuda, and T. Takahashi, *Tetrahedron*, **27**, 5147 (1971); d) T. Murae, A. Sugie, T. Tsuyuki, S. Masuda, T. Takahashi, *ibid.*, **29** 1515 (1973).

2) a) H. Hikino, T. Ohta, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **18**, 219, 1082 (1970); b) *Idem, ibid.*, **19**, 212, 2203, 2211, 2651 (1971).

3) Z. Valenta, S. Papadopoulos, and C. Podešva, *Tetrahedron*, **15**, 100 (1961); Z. Valenta, A. H. Gray, D. E. Orr, S. Papadopoulos, and C. Podešva, *ibid.*, **18**, 1433 (1962); W. A. C. Brown and G. A. Sim, *Proc. Chem. Soc.*, **1964**, 293.

4) The PMR spectra of XVII and XVIII had been determined in pyridine by Hikino *et al.*[2b)] Measurements in $CDCl_3$ were effected for the present communication.

5) *Cf.* N. S. Bhacca and D. H. Williams, "Application of NMR Spectroscopy in Organic Chemistry," Holden-Day Inc., San Francisco (1964), Chapter 2.

6) *Cf.* J. M. Lehn and G. Ourisson, *Bull. Soc. Chim. Fr.*, **1962**, 1137; Y. Tanahashi, Y. Moriyama, T. Takahashi, F. Patil, and G. Ourisson, *ibid.*, **1966**, 2374, and references therein.

7) PMR spectral measurements using $Eu(dpm)_3$ as a shift reagent resulted in coordinations of the reagent to at least two positions of a compound. The obtained spectra gave no information.

8) B. Viala and J. Polonsky, *C. R. Acad. Sci. Paris, C*, **271**, 410 (1970).

When a hydroxyl group is located on C-13, this methyl signal is shifted downfield ($\Delta+0.20$—$+0.27$ ppm) and resonates as a singlet (compare V with III, VI with II, XII with I, and X with XVII). An introduction of a double bond between C-14 and C-15 causes a downfield shift ($\Delta+0.26$ ppm) of this methyl signal (compare IX with VI).

The signal due to an olefinic methyl group at C-13 appears at δ 1.83—1.91 as a singlet for the compounds with a methylated diosphenol moiety in ring C (IV, XIV, and XVI). This olefinic methyl signal is shifted downfield ($\Delta+0.15$ ppm) on introduction of a double bond between C-14 and C-15 (compare XXI with IV).

Practically, no effect is observed for the signal due to the methyl group at C-13, when a structural change is effected in ring A.

Methyl Group at C-10. A tertiary methyl group at C-10 appears at δ 1.40—1.50 as a singlet when the substituent at C-11 is a hydroxyl group (I, II, VI, VII, IX, XI—XIII, XV, and XX). Similar chemical shift values are observed for the methyl signal of the compounds with a methylene dioxy grouping (δ 1.43—1.47; X, XVII, and XVIII), and for the signal of the substances with a methylated diosphenol moiety in ring C (δ 1.45—1.54; IV, XIV, XVI, and XXI).

The signal due to the methyl group at C-10 is not affected by introduction of a hydroxyl group at C-13 (compare V with III, and VI with II) nor by location of a hydroxyl group on C-14 (compare VII with VI). An upfield shift ($\Delta-0.14$—-0.20 ppm) is observed for this methyl signal on acetylation of the hydroxyl group at C-11 (compare III with II, V with VI, and VIII with XX). Practically, no effect is observed for this signal on methylation of the hydroxyl group at C-12 (compare II with I, and VI with XII).

Methyl Group at C-8. A singlet at δ 1.16—1.28 is observed for a tertiary methyl group at C-8 of the compounds with both a hydroxyl (or an acetoxyl) group at C-11 and the substituent R_3=H (I—III, VIII, XI, XV, XIX, and XX).

An introduction of a hydroxyl group at C-13 causes a downfield shift ($\Delta+0.24$—$+0.29$ ppm) of the signal due to the methyl group at C-8; this methyl group and the hydroxyl group at C-13 are in a 1,3-diaxial relationship (compare V with III, VI with II, XII with I, and X with XVII). Some downfield shifts are observed for this methyl signal on acetylation of the hydroxyl group at C-11 ($\Delta+0.06$—$+0.07$ ppm; compare III with II, V with VI, and VIII with XX), on formation of a methylene dioxy ring ($\Delta+0.07$ ppm; compare X with VI, and XVII with II), and on introduction of a double bond between C-14 and C-15 ($\Delta+0.04$—$+0.09$ ppm; compare IX with VI, and XXI with IV). The methyl signal suffers some upfield shifts when a hydroxyl group is substituted on C-14 ($\Delta-0.04$—-0.11 ppm; compare VII with VI, XI with I, and XVIII with XVII), and when a hydroxyl group at C-12 is methylated ($\Delta-0.03$—-0.07 ppm; compare II with I, and VI with XII). Replacement of a lactone grouping in ring D by a hemiacetal moiety causes an upfield shift ($\Delta-0.08$—-0.13 ppm) of this methyl signal (compare VI with XIII, I with XV, and IV with XIV). The signal due to the methyl group at C-8 is not affected by a structural change in ring A (compare II with XX, III with VIII, and III with XIX).

Nigakihemiacetal D. As an example of application of the result shown above, the structure determination of a new bitter principle, nigakihemiacetal D (XXIII), isolated recently from *Picrasma ailanthoides* Planchon is described.

The presence of an acetoxyl, a hydroxyl and two methoxyl groups, one secondary and three tertiary methyl groups, and a hemiacetal[1c)] and an α,β-unsaturated ketone[1a)] moieties was suggested for XXIII from its spectral data (Experimental) and the molecular formula ($C_{24}H_{36}O_8$). As the spectral data of XXIII are similar to those of bitter substances hitherto isolated[1)] from the same plant, XXIII is assumed to be a hemiacetal derivative related to the quassolidane (XXII).

As the methyl groups at C-8 and C-10 are tertiary ones (*Cf.* XXII), a secondary methyl resonating at δ 1.03 (J=7 Hz) must locate on either C-4 or C-13; the latter case is excluded as shown later. Therefore, this signal can be assigned to the methyl group at C-4 (not on a saturated ring A) (*Cf.* I—VII, IX—XV, XVII, XVIII, XXI). A tertiary methyl signal at δ 1.20 can be best assigned to the methyl group at C-13 to which a hydroxyl group is substituted (*Cf.* V—VII, XII, XIII). Chemical shift value (δ 1.36) observed for another tertiary methyl signal shows that this methyl group is in a 1,3-diaxial relationship with the hydroxyl group at C-13 and located on C-8 (*Cf.* XIII; with a hemiacetal grouping in ring D). The UV maximum at 262.5 nm[1a,c)] of XXIII provides support for the location of an acetoxyl group on C-11. Thus a tertiary methyl signal at δ 1.24 could be assigned to the methyl group at C-10 (*Cf.* III, V; with an acetoxyl group at C-11).

These observations can be well interpreted based on a hemiacetal structure related to nigakilactone E (V) and lead to the structure XXIII for nigakihemiacetal D. This was confirmed by the formation of nigakilactone E (V)[1a)] on oxidation of this hemiacetal (XXIII) with silver oxide.

Experimental

PMR spectra were taken on a JEOL JNM-C-60 spectrometer at 60 MHz in $CDCl_3$ solution containing TMS as an internal standard.

Isolation of XXIII. Extraction and subsequent separation procedures of crude material (200 g) from the stemchips (160 kg) of *Picrasma ailanthoides* Planchon were decribed elsewhere.[1d)] After chromatographic separation of the fractions 2 and 3[1d)] containing picrasin D, the Fractions 4—6 were eluted with acetone-benzene (1: 2) to give nigakihemiacetal D (XXIII) (15 mg), amorphous solid, $[\alpha]_D+46°$ (*c* 0.1, MeOH); UV (MeOH): λ_{max} 262.5 nm (ε 2000), IR (Nujol): 3450, 1735, 1708, 1640, 1245 cm^{-1}; PMR ($CDCl_3$): δ 1.93 (3H, s; $-OCOC\underline{H}_3$), δ 3.27 (1H, d, J=9 Hz, $-\overset{|}{C}\underline{H}OCH_3$), δ 3.51 (3H, s; $-OC\underline{H}_3$), δ 3.56 (3H, s; $-OCH_3$), δ 3.72 [1H, m; $-\overset{|}{C}\underline{H}-O-CH(OH)-$], δ 5.44 (1H, q; J=11 and J=9 Hz; $-\overset{|}{C}\underline{H}-OCOCH_3$), δ 5.07 (1H, d, J=2.5 Hz; $-\overset{|}{C}=\overset{|}{C}\underline{H}$).

Oxidation of XXIII with Silver Oxide. Compound XXIII (10 mg) was treated with silver oxide as usual[1d)] to give nigakilactone E (V)[1a,b)] (7mg) identified by IR, PMR, $[\alpha]_D$ and tlc.