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Solvent Shifts of Methyl Proton Resonances of Pinanols and Related Compounds[1]

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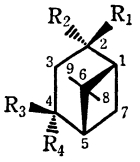
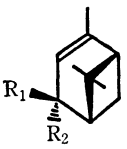
The chemical shifts of methyl protons of a number of bicyclo[3.1.1]heptanols and their acetates were measured on carbon tetrachloride and benzene in order to examine the correlation between the benzene-induced shifts and the spatial arrangements of the functional groups concerned. Thus, the shifts induced by benzene were found to be useful in establishing both the location and the stereochemistry of methyl protons situated in the vicinity of the hydroxyl or the acetoxyl function in a pinane skeleton.

It has been reported[3-10] that solvent shifts (Δ) of proton resonances can be used in the elucidation of stereochemical problems. Particularly, the empirical rule[3-6] for ketones has been useful in considering these problems. However, attempts to extend the rule to alcohols and their acetates and to find a generalization in these fields have not been successful. In connection with our studies of the stereochemistry and the reaction of pinane derivatives, significant solvent effects were found for the methyl protons of pinanols and their acetates. The author now wishes to report his findings regarding the benzene-induced shifts and to correlate the shifts with the stereochemistry of the functional groups concerned.

Results and Discussion

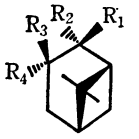
The benzene-induced shifts ($\Delta=\delta_{CCl_4}-\delta_{C_6H_6}$) were measured for three methyl protons in pinanols

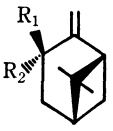




1: R_1=OH, R_2=CH_3, R_3=R_4=H
2: R_1=CH_3, R_2=OH, R_3=R_4=H
3: R_1=OH, R_2=R_3=R_4=H
4: R_1=R_3=R_4=H, R_2=OH
5: R_1=CH_3, R_4=R_1=H, R_3=OH
6: R_1=CH_3, R_2=R_3=H, R_4=OH
15: R_1=OAc, R_2=R_3=R_4=H
16: R_1=R_3=R_4=H, R_2=OAc
17: R_1=CH_3, R_2=R_4=H, R_3=OAc
18: R_1=CH_3, R_2=R_3=H, R_4=OAc

7: R_1=OH, R_2=H
8: R_1=H, R_2=OH
19: R_1=OAc, R_2=H
20: R_1=H, R_2=OAc





9: R_1=CH_3, R_2=R_4=H, R_3=OH
10: R_1=CH_3, R_2=R_3=H, R_4=OH
11: R_1=R_4=H, R_2=CH_3, R_3=OH
12: R_1=R_3=H, R_2=CH_3, R_4=OH
21: R_1=CH_3, R_2=R_4=H, R_3=OAc
22: R_1=CH_3, R_2=R_3=H, R_4=OAc
23: R_1=R_4=H, R_2=CH_3, R_3=OAc
24: R_1=R_3=H, R_2=CH_3, R_4=OAc

13: R_1=OH, R_2=H
14: R_1=H, R_2=OH
25: R_1=OAc, R_2=H
26: R_1=H, R_2=OAc

and their acetates, which have a known configuration, as is depicted. The results indicated that, in all the cases examined, the 8-methyl protons suffered increased shielding to a considerably large extent, as is shown in Table 1. On the other hand, the methyl

1) This paper forms Part XIX[2] in the Hiroshima University series on "Stereochemical Studies of Monoterpene Compounds."
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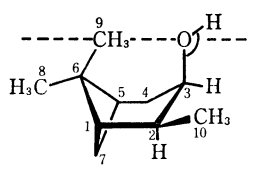
TABLE 1. VALUES (δ_{CCl_4}-$\delta_{C_6H_6}$ ppm) FOR METHYL PROTON RESONANCES AT THE 8-, 9-, AND 10-POSITIONS IN HYDROXYPINANES AND THEIR ACETATES

Compd	$\Delta\delta_{CCl_4-C_6H_6}$ (ppm)		
	C-8	C-9	C-10
2β-hydroxy-10α-pinane (**1**)	+0.09	−0.03	+0.07
2α-hydroxy-10β-pinane (**2**)	+0.09	+0.11	+0.04
2β-hydroxyapopinane (**3**)	+0.05	−0.04	—
2α-hydroxyapopinane (**4**)	+0.10	+0.14	—
4β-hydroxy-10β-pinane (**5**)	+0.02	−0.02	+0.05
4α-hydoxy-10β-pinane (**6**)	+0.10	+0.11	+0.07
4β-hydroxy-pin-2-ene (**7**)	+0.08	−0.07	+0.12
4α-hydroxy-pin-2-ene (**8**)	+0.13	+0.07	+0.13
3β-hydroxy-10β-pinane (**9**)	+0.06	−0.06	0.00
3α-hydroxy-10β-pinane (**10**)	+0.07	+0.11	+0.01
3β-hydroxy-10α-pinane (**11**)	+0.07	0.00	+0.01
3α-hydroxy-10α-pinane (**12**)	+0.08	+0.10	0.00
3β-hydroxy-pin-2(10)-ene (**13**)	+0.13	−0.01	—
3α-hydroxy-pin-2(10)-ene (**14**)	+0.12	+0.06	—
2β-acetoxyapopinane (**15**)	+0.12	+0.04	—
2α-acetoxyapopinane (**16**)	+0.16	+0.18	—
4β-acetoxy-10β-pinane (**17**)	+0.10	−0.01	+0.11
4α-acetoxy-10β-pinane (**18**)	+0.18	+0.25	+0.15
4β-acetoxy-pin-2-ene (**19**)	+0.12	−0.12	+0.19
4α-acetoxy-pin-2-ene (**20**)	+0.21	+0.14	+0.20
3β-acetoxy-10β-pinane (**21**)	+0.10	−0.01	−0.01
3α-acetoxy-10β-pinane (**22**)	+0.14	+0.19	+0.01
3β-acetoxy-10α-pinane (**23**)	+0.14	+0.05	+0.02
3α-acetoxy-10α-pinane (**24**)	+0.09	+0.17	−0.03
3β-acetoxy-pin-2(10)-ene (**25**)	+0.17	−0.02	—
3α-acetoxy-pin-2(10)-ene (**26**)	+0.15	+0.13	—

protons at the 9-position showed a different value of shifts, in dependence on the spatial arrangements between the functional group and the *gem*-dimethyl bridge. Shifts to a lower field were noted for a *cis*-form, and to a higher one, for a *trans*-form. The downfield shifts have been observed[9] for monohydroxysteroids in which the hydroxyl and the methyl groups are 1,3-diaxial. We observed the same phenomena for 2- or 4-hydroxypinanes and their acetates respectively. For *cis*-3-hydroxypinanes and their acetates, also, downfield shifts or very small upfield shifts were observed, although the 9-methyl and the hydroxyl groups are not perfectly 1,3-diaxial but, rather, those are situated in a nearly diaxial arrangement, as is shown in **9a**. Therefore, it is very likely that the 9-methyl



9a

protons of *cis*-3-hydroxypinanes and their acetates suffer decreased shielding by benzene. These observations suggest that the unknown configuration of a hydroxyl or acetoxyl group of pinane derivatives can probably be determined by measuring the benzene-induced shifts of the methyl protons at the 9-position.

On the modification of the rule[3-6] established for ketones, an empirical rule can thus be proposed on the bases of the above observations and the data reported for hydroxy-steroids.[9] As an aid for predicting the benzene-induced shifts, a reference plane is imagined through the hydroxyl oxygen atom at right angles to the carbon-oxygen bond of the hydroxyl group. The Δ values are negative for protons lying on the reference plane; they become positive as they leave the plane. The bonzene-induced shifts of the hydroxylated or the acetoxylated pinane derivatives may be useful in establishing both the location and the stereochemical relationship of protons situated in the vicinity of the hydroxyl or the acetoxyl function.

Experimental

The NMR spectra were measured with a Varian Associates HA-100 spectrometer and a Hitachi Perkin-Elmer R-20 high-resolution spectrometer on the carbon tetrachloride and the benzene solution in a 5% (w/v) concentration at normal probe temperatures (*ca.* 30°C), using tetramethylsilane as the internal standard. The chemical shifts of the proton resonances of the 8-, 9-, and 10-methyl protons of pinanols and their acetates are shown in Table 2, expressed in δ-values (accuracies, $\pm$0.02 ppm). The purity of the samples used was checked by a combination of thin-layer chromatography with silica gel and vapor-phase chromatography using a Hitachi Perkin-Elmer F6-D Gas Chromatagraph with a stainless-steel column (3 mm$\times$1 m) packed with 20% PEG-6000 on Celite (60—80 mesh) at 120—150°C. All the spectral data (IR, NMR and MS) and physical properties of each sample coincided with those of the data reported in the literature and completely supported the structure depicted above.

The 2-hydroxypinanes, (**1**) and (**2**), were generously donated by Ohloff,[11] while the hydroxypinanes, (**5**), (**9**), (**10**), (**11**) and (**12**), had been previously synthesized in our laboratory by the reduction of the appropriate ketones.[12-14] Most of the acetates were prepared from the corresponding alcohols by treating them with acetic anhydride in pyridine, followed by purification with preparative thin-layer chromatography on silica gel, using a mixture of *n*-hexane and ethyl acetate as solvent.

*2-Hydroxyapopinanes (**3**) and (**4**).* A mixture of 1.0 g of (+)-nopinone ($[\alpha]_D^{25}$+20.3°, prepared from (−)-β-pinene by ozonization), 2.6 g of aluminum isopropoxide, and 20 m*l* of isopropyl alcohol was refluxed for 4 hr, and then worked-up following the method in the literature.[15] The oily product (910 mg) thus obtained was subjected to column chromatography on silica gel with a mixture of ethyl acetate and *n*-hexane to give 334 mg of 2β-hydroxyapopinane (**3**) (mp 103.5—104.0°C, lit,[15] mp 101.5—102.0°C; $[\alpha]_D^{25}$−12.0° (*c* 0.75, MeOH); the phthalate, mp 131.0—131.5°C, lit,[15] mp 131.0—131.5°C) and 175 mg of the 2α-epimer (**4**) (mp 35—36°C, lit,[15] mp 37.0—37.5°C; $[\alpha]_D^{25}$−15.2° (*c* 0.67,

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Table 2. Chemical shifts (δ_{ppm}) of methyl proton resonances of hydroxypinanes and their acetates in carbon tetrachloride and benzene

Compd	CCl_4			C_6H_6		
	C-8	C-9	C-10	C-8	C-9	C-10
1	1.23	1.10	1.25	1.14	1.13	1.18
2	1.27	0.94	1.46	1.18	0.83	1.23
3	1.23	1.10	—	1.18	1.14	—
4	1.26	0.84	—	1.16	0.70	—
5	1.26	1.19	1.07	1.24	1.21	1.02
6	1.26	0.99	1.00	1.16	0.88	0.93
7	1.34	1.04	1.71	1.26	1.11	1.59
8	1.33	0.87	1.72	1.20	0.80	1.59
9	1.17	1.05	1.05	1.11	1.11	1.05
10	1.24	0.95	1.11	1.17	0.84	1.10
11	1.23	0.92	1.00	1.16	0.92	0.99
12	1.22	0.77	0.94	1.16	0.67	0.94
13	1.28	0.76	—	1.15	0.77	—
14	1.30	0.66	—	1.18	0.60	—
15	1.24	1.06	—	1.12	1.02	—
16	1.22	0.87	—	1.06	0.69	—
17	1.23	1.11	1.06	1.13	1.12	0.95
18	1.28	1.07	1.05	1.10	0.84	0.90
19	1.34	0.98	1.72	1.22	1.12	1.53
20	1.36	0.94	1.74	1.15	0.80	1.54
21	1.18	1.01	0.94	1.08	1.02	0.95
22	1.22	0.99	1.08	1.08	0.80	1.07
23	1.21	0.90	0.96	1.07	0.85	0.94
24	1.20	0.80	0.82	1.11	0.63	0.85
25	1.27	0.78	—	1.10	0.80	—
26	1.29	0.72	—	1.14	0.59	—

MeOH); the phthalate, mp 154—155°C, lit,[15] mp 155.8—156.2°C).

*4β-Hydroxy-pin-2-ene(**7**).* The reduction of 680 mg of (−)-verbenone ($[\alpha]_D^{25}$−208.6°, prepared from (−)-α-pinene by *t*-butyl chromate oxidation) with 200 mg of sodium borohydride gave 600 mg of a crude sample of Compound **7**; this sample was purified by recrystallization followed by preparative gas chromatography with a PEG-6000 column; mp 67—68°C (lit,[16] mp 68—70°C); $[\alpha]_D^{25}$−17.3° (*c* 0.75, MeOH) (lit,[16] $[\alpha]_D^{22}$−16.0°).

*4α-Hydroxy-pin-2-ene (**8**) and Its Acetate (**20**).* Following the procedure previously reported,[17] (−)-α-pinene (3.0 g; $[\alpha]_D^{25}$−39.9°) was oxidized with lead tetraacetate in dry benzene. The oxidation product (2.95 g) was isomerized with glacial acetic acid to give an oily product (2.90 g). Purification by column chromatography on silica gel gave the acetate (**20**) (1.55 g) ($[\alpha]_D^{25}$−128.1° (*c* 1.00, MeOH), lit,[16] $[\alpha]_D^{22}$−135.6°; IR (liq.) 1735 ($OCOCH_3$) and 1650 cm^{-1} (C=C)). The saponification of the acetate (**20**) (0.7 g) with methanolic sodium hydroxide gave the alcohol (**8**) (0.45 g) ($[\alpha]_D^{25}$−107.2° (*c* 0.78, MeOH), lit,[16] $[\alpha]_D^{22}$−112.7°; the *p*-nitrobenzoate; mp 98—99°C, lit,[16] mp 98—98.5°C).

*4α-Hydroxy-10β-pinane (**6**).* The hydrogenation of 4α-hydroxy-pin-2-ene (**8**) (250 mg) in the presence of the Adams catalyst (10 mg) in cyclohexane gave the pinanol (**6**) (249 mg); mp 85—86°C (lit,[12] mp 87°C).

*3β-Hydroxy-pin-2(10)-ene (**13**).* Following the procedure previously reported,[18] pinocarvone (7.0 g; bp 69.0—70.0°C (6.5 mmHg), $[\alpha]_D^{25}$+55.1°, n_D^{25} 1.4959, d_4^{25} 0.9952), which had been prepared from (−)-β-pinene by selenium dioxide oxidation,[18] was treated with bromine and then zinc powder in acetic acid to yield 3β-hydroxy-pin-2(10)-ene (**13**) (3.4 g); mp 49—50°C (lit,[18] mp 50—50.5°C), $[\alpha]_D^{25}$−37.4° (*c* 3.6, MeOH) (lit,[18] $[\alpha]_D$−41°).

*3α-Hydroxy-pin-2(10)-ene (**14**) and Its Acetate (**26**).* Lead tetraacetate (10 g) was added, over 10-min periods, to a stirred suspension of calcium carbonate (1.0 g) in dry benzene (50 m*l*) containing (−)-β-pinene (5.0 g; $[\alpha]_D^{25}$−20.0°); the mixture was then stirred at 60°C for a further 30 min. The reaction mixture was worked up as usual to afford an oily product, which was then subjected to column chromatography on silica gel with a mixture of *n*-hexane and ethyl acetate to give 3α-acetoxy-pin-2(10)-ene (**26**) (3.2 g) ($[\alpha]_D^{25}$−15.9° (*c* 12.8, MeOH), n_D^{25} 1.4739, d_4^{25} 0.9894). The saponification of the acetate (**26**) (0.6 g) with methanolic potassium hydroxide gave the alcohol (**14**) (0.4 g) ($[\alpha]_D^{25}$+60.7° (*c* 1.61, MeOH), lit,[18] $[\alpha]_D$+60°).

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