Jesromotetrol Carbon-13 Nuclear Magnetic Resonance. Boric and Phenylboronic Acids as Assignment Aids for 1,2- and 1,3-Diols[1]

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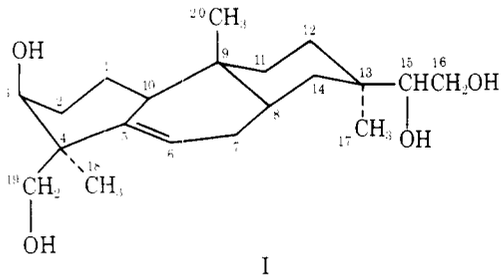
The addition of boric acid or phenylboronic acid to either 1,2- or 1,3-diols has been shown to produce substantial alterations in the ^{13}C chemical shifts of the parent compounds. In the case of either reagent the cyclic cis diols react to the exclusion of the trans isomer. Boric acid induced shifts are comparable to acetylation shifts. The ^{13}C lines of the diterpene jesromotetrol have been assigned with the aid of boric acid induced shifts.

Jesromotetrol (I) has been isolated from *Palafoxia rosea* (Compositae) by Dominguez and co-workers and shown by X-ray techniques to be a diterpene of the structure I by Zabel



I

and Watson.[2] The ^{13}C chemical shifts were obtained on a small sample of I and reported previously[2] without assignment. Because of the rather unique stereochemical features of the molecule (i.e., the axial hydroxy and methyl groups at carbons 3 and 4) and the presence of both 1,2- and 1,3-diol structures, it seemed particularly worthwhile that the ^{13}C assignments for the molecule be made. A further challenge was added by this latter factor, for one would expect that both ends of the molecule would react with lanthanide chemical shift reagents to produce a generally noninformative pattern of lanthanide induced shifts (LIS).

Böeseken[3] some years ago reviewed the work of his research group on the formation of complexes by 1,2-glycols and boric acid. He reported at that time that no complexes were formed by 1,3-diols, a statement which has been repeated in later literature. Based on this observation, it appeared that selective complexation of the 1,2-diol end of jesromotetrol might be effected and any changes in the ^{13}C NMR spectrum might then be used to assign the lines. In retrospect, it can be noted here that Hermans[4] had reported that borate esters formed more readily from 1,3-diols than from 1,2-diols. This conclusion was subsequently substantiated by Hubert, Hargitay, and Dale, who concluded that cyclic 1,2-diol borate esters rearrange to mixtures of linear polymeric borates on distillation.[5]

Reported here are the chemical shifts and boric acid induced shifts for a group of simple 1,2- and 1,3-diols. Similar data are given also for the esters of phenylboronic acid.[6] Finally, the boric acid induced shifts, acetylation shifts, and LIS were utilized to complete the assignments of jesromotetrol.

Experimental Section

The ^{13}C NMR spectra reported here were acquired on a JEOL FX-60 operating in the FT mode at 15 MHz with an 8K transform. All chemical shifts are in parts per million with reference to tetramethylsilane. Single-frequency decoupling (sford) was accomplished with the decoupling oscillation set 5 ppm upfield from the proton frequency of Me_4Si. Partially relaxed spectra (PRFT) were used for the assignments of methylene, methine, quaternary, and methyl carbons of jesromotetrol as only limited data were obtained by the sford experiments.

Propylene glycol, *cis*- and *trans*-1,2-cyclohexanediol, *cis*- and *trans*-1,3-cyclohexanediol, and 1,3-butanediol were all commercially available materials, as was the phenylboronic acid. Synthesized glycols were 1,1-dimethylethylene glycol,[7] 1,1,2-trimethylethylene glycol,[8] and *tert*-butylethylene glycol.[9] The latter was prepared by the acid-catalyzed hydrolysis of *tert*-butylethylene oxide, which in turn was prepared from *tert*-butylethylene and *m*-chloroperbenzoic acid in methylene chloride at 25 °C.

A sample of 2-(hydroxymethyl)-2-methylcyclohexanol was prepared by the lithium aluminum hydride reduction of ethyl 1-methyl-2-oxocyclohexanecarboxylate.[10] An X-ray structure of this material was kindly performed by Drs. W. H. Watson and J. S. Chen on a sample crystallized from 1:1 benzene–petroleum ether, mp 87–89 °C (lit.[10] mp 89 °C). The hydroxymethyl and ring hydroxy groups are trans and diequatorial. The ^{13}C NMR data are given in Table II. The diacetate was prepared in situ and not further characterized.

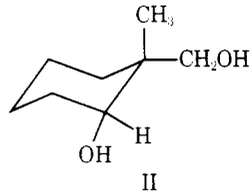
A sample of 1-bromo-1-methylcyclohexane was prepared from the corresponding alcohol. The bromide, unstable to light, was reluctant in forming a Grignard reagent in ether. Upon several attempts under a variety of conditions, only starting material and/or a mixture of olefins was recovered.

At two points in time 20-mg samples of jesromotetrol were provided by X. A. Dominguez of the Instituto Tecnologico de Monterrey, to whom appreciation is expressed. Jesromotetrol has no appreciable solubility in chloroform, but is quite soluble in 10% pyridine in chloroform. Following the determination of the normal, sford, and PRFT spectra in the mixed solvent (1 mL), $Yb(fod)_3$ was added in small increments and the spectra were redetermined. The tetrol was recovered by addition of excess chloroform, which retained the lanthanide in solution but precipitated the diterpene. The diterpene spectrum was then redetermined in 10% pyridine–chloroform followed by the addition of about 50 mg of boric acid. The boric acid induced shifts were determined from normal and PRFT spectra. The known tetraacetate[2] was generated in situ by treating the solution with acetic anhydride and allowing it to stand overnight. The solution was evaporated to dryness under vacuum, and the tetraacetate was extracted with a small amount of deuteriochloroform, in which it is soluble.

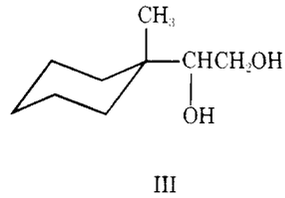
Results and Discussion

Jesromotetrol has the carbon skeleton of the rimuene diterpenes for which no ^{13}C assignments appear to have been made. The carbons can be sorted as to type by the use of off-resonance decoupling and partial relaxation techniques. Beyond this, however, one must resort to the use of model compounds, chemical shift reagents, and chemical modifications of the structure (i.e., deuterium substitution, acetylation shifts, or other alterations of structure). Structure-chemical shift additivity principles are as yet too imprecise to allow predictions for a molecule of such complexity.

As noted in the Experimental Section, attempts to synthesize the model compounds II and III were not successful.



II



III

0022-3263/79/1944-1631$01.00/0

Table I. Chemical Shifts (ppm) of Various Glycols in Perdeuteriopyridine and Effects ($\Delta\delta$) of Added Boric Acid (A) and/or Phenylboronic Acid (B)

	registry no.	C-1	C-2	methyl (s)	
propylene glycol	57-55-6	68.4	68.4	19.9	
A	10043-35-3	0.6	0.2	−0.1	
B	98-80-6	1.6	1.0	0.3	
1,1-dimethylethylene glycol	558-40-3	70.8	71.4	26.6	
A		1.0	1.6	0.4	
B				0.7	
tert-butylethylene glycol	59562-82-2	63.2	79.83	26.1	
A[a]		1.1	1.4	−0.7	
1,1,2-trimethylethylene glycol	5396-58-7	72.6	74.2	18.2 (2), 24.7 (1), 26.1 (1)	
A		7.2	5.4	−1.0, −1.4, 2.3	
B		9.6	7.4	−1.1, −1.5, 2.3	
tetramethylethylene glycol	76-09-5	74.5	74.5	25.3	
A		7.4	7.4	−0.8	
B		9.3	9.3	−0.3	
				C-3	C-4
1,3-butanediol	107-88-0	59.8	42.4	65.4	24.2
B		1.4	−8.0	2.3	−1.0
cis-1,2-cyclohexanediol	1792-81-0	70.8	70.8	29.9	21.6
A		0.2	0.2	−0.3	−0.1
B		4.8	4.8	−1.2	−1.3
				C-4	C-5
cis-1,3-cyclohexanediol	823-18-7	68.7	46.0	35.6	21.1
A		−1.6	−12.0	−3.9	−6.0

[a] Quaternary C, 33.7 ppm; the affect of added boric acid is nil.

Table II. ^{13}C Assignments, LIS, and Acetylation and Boric Acid Induced Shifts for *trans*-2-(Hydroxymethyl)-2-methylcyclohexanol[a]

carbon	δ	rel LIS	$\Delta\delta$(OAc)	$\Delta\delta(H_3BO_3)$
1	77.0	0.83	−3.6	2.6
2	39.3	0.77	−1.3	−4.6
3	33.5	0.28	0.1	−0.9
4	20.6	0.16	0.2	−1.0
5	24.7	0.15	−0.6	−0.6
6	30.3	0.32	−3.4	−2.5
CH_2OH	74.7	1.00	−4.9	−2.9
CH_3	13.6	0.55	2.0	−0.9

[a] All data were taken in deuteriochloroform except those for the boric acid induced shifts, which are for pyridine as solvent. Registry no. *trans*-2-(hydroxymethyl)-2-methylcyclohexanol, 69551-50-4.

Table III. Chemical Shifts (ppm), Acetylation and Boric Acid Shifts, and Relative LIS for Jesromotetrol[a]

carbon	δ	$\Delta\delta$(HOAc)	$\Delta\delta(H_3BO_3$	rel LIS
1	18.7	0.3	0.0	0.10
2	28.9	−1.9	−1.6	0.06
3	75.6	1.1	0.6	0.15
4	43.9	−3.1	−3.1	0.14
5	139.5			
6	120.3			0.13
7	30.7	−0.1	−0.1	0.10
8	35.8			0.13
9	35.1	−0.1	0.0	0.11
10	46.6	−0.5	−0.6	0.10
11	33.9	−0.3	−0.2	0.13
12	29.2	−0.2		0.22
13	36.5	−0.2		0.40
14	36.5	0.0	0.2	0.20
15	80.9	4.0	3.1	0.95
16	62.1	1.1	2.8	1.00
17	18.5	0.6	−0.6	0.20
18	24.5	−1.8	−1.8	0.08
19	70.0	−0.9	−1.0	0.18
20	12.3	0.0	0.0	0.08

[a] Solvent was 10% perdeuteriopyridine in deuteriochloroform except for the tetraacetate, which was in deuteriochloroform. Registry no. jesromotetrol, 67911-60-8.

However, the trans isomer of II was prepared, the geometry was determined by X-ray crystallography, and the results of a ^{13}C NMR analysis are reported subsequently. As an approximation to III, *tert*-butylethylene glycol was prepared and the assignments are given in Table I. Examination of the jesromotetrol structure I shows that carbons 1, 7, 8, 9, 10, 11, 12, 14, and 20 are related to carbons 11, 6, 5, 10, 9, 1, 2, 4, and 19, respectively, of 3β-hydroxy-7,22-ergostadiene, which have been assigned[11] and which can serve as a useful model compound here.

As mentioned previously, the application of boric acid induced shifts in the ^{13}C spectrum of jesromotetrol was contemplated, and the data subsequently given in Table III indicate that a number of carbons are affected by borate formation. In order to utilize these data, a study was undertaken of the effects of boric acid esterification on the ^{13}C spectra of a number of glycols. The data for these glycols, their borate esters, and their phenylboronic acid esters are given in Table I. For propylene glycol and 1,1-dimethylethylene glycol the principal observation was a marked broadening of the lines associated with the hydroxyl-bearing carbons. As pointed out in the literature,[5] simple 1,2-diols form linear polymers with boric acid. However, as steric hindrance increases, the formation of cyclic esters occurs. At room temperature boric acid does not seem to react with *cis*-1,2-cyclohexanediol, a result in keeping with an earlier measurement of electrical conductivity.[12] In keeping also with earlier studies,[6] phenylboronic acid reacts readily at room temperature. Phenylboronic acid has the added advantage that both it and its cyclic esters are soluble in chloroform. Boric acid is best used in pyridine or in pyridine–chloroform mixtures.

The effects on ^{13}C chemical shifts of either boric or phenylboronic acids resemble closely those of acetylation, i.e.,

deshielding at the α carbon and shielding at the β carbon. This point is emphasized later on by the comparative results for jesromotetrol. In both 1,3-butanediol and *cis*-1,3-cyclohexanediol the intervening methylene experiences a marked upfield shift. The acetylation shift for the C-2 methylene in 1,3-butanediol is −5.7 ppm, which presumably reflects a doubling of the β-effect alteration which occurs upon acetylation.

The latent potential of using boric acid type shifts in stereochemical studies should be pointed out. In trimethylethylene glycol, cyclic borate formation will require that two methyls at C-1 and C-2 become eclipsed, while the third methyl suffers no such steric interaction. The experimental observation is that two methyls do, in fact, show an enhanced shielding γ-type interaction while the third moves downfield. A similar result is found for C-5 in the *cis*-1,3-cyclohexanediol; i.e., in the free diol both hydroxyls are equatorial, but these are forced to become diaxial in the borate ester. The two resultant γ interactions cause C-5 to move 6 ppm upfield.

The hydroxy and hydroxymethyl groups of *trans*-II are equatorial from the X-ray crystal structure, and it may be presumed that this conformer is prevalent in solution also. The ^{13}C line assignments (Table II) for *trans*-II were based on the LIS and boric acid induced shifts. The latter values agree with the results in Table I in that the α effect of borate formation is deshielding while the β effect is shielding and about doubled at carbon-2. However, acetylation shifts for this molecule are atypical. The α carbons become strongly shielded upon acetylation, and the β effect at C-2 is reduced in magnitude. These results suggest a major conformational change in *trans*-II upon acetylation, placing both the acetoxy and acetoxymethyl groups in axial positions. The resultant new 1,3-diaxial interactions account for the abnormal shieldings observed. This conjecture is substantiated by the downfield shift of the C-2 methyl since the proposed conformational alteration would move this methyl from an axial to an equatorial position.

The assignments for jesromotetrol (Table III) depend on a complex of data from the model compounds mentioned previously and the LIS and boric acid induced shifts given in Table III. The assignment of C-15 and C-16 follows from *tert*-butylethylene glycol. The hydroxyls on these carbons compete more favorably for the lanthanide shift reagent than those at C-3 and C-19. This may reflect differences in the steric environment at these positions or geometric factors which make a 1,2-diol more able to complex over the type of 1,3-diol structure found here. The situation is made somewhat more complex by the presence of pyridine as a solvent component as this too may compete for lanthanide binding sites. There is no reason to believe that the falloff of LIS with distance from the site of hydroxyl complexation would be grossly modified by the presence of pyridine, and qualitative arguments based on the LIS should still be valid. Thus, one can assign the three methyls on the basis of their LIS and the fact that C-20 should be very similar to the ergostadienol C-19 value. The formation of the borate esters would be expected to produce perturbations in the order C-18 > C-17 > C-20, as was observed.

For the three quaternary carbons, C-4 would be expected to show a large shielding change upon reaction with boric acid or acetylation. The esterification effects at C-13 should be less than those at C-4 but larger than those at C-9. The LIS for C-13 is found to be, as expected, the largest of the three.

In general, methyl and hydroxyl groups provide γ-gauche shielding interactions of closely similar magnitude (~4–6 ppm). Methine carbons 8 and 10 can be assigned by analogy with the ergostadiene, provided allowance is made for the γ interaction of the 17-methyl on C-8. Similar considerations of the methylene carbons with reference to the steroid model, LIS, and allowing for the appropriate γ interactions at carbons 1, 2, and 11 lead to the values given in Table III as well.

As will be noted, acetylation and boric acid induced shifts in jesromotetrol are of similar magnitude and sense. Both reagents suffer in that their effects are all or nothing results. Thus, it is difficult to sort out the five lines in the jesromotetrol spectrum which fall in the 34–36 ppm region. Since the lanthanide induced shifts can be altered in increments, the tracking of lines is more certain. The above examples, however, would seem to establish the utility of boric acid and phenylboronic acid as reagents for assisting in the assignment of ^{13}C lines for *cis*-1,2- and *cis*-1,3-diols.

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Registry No.—*trans*-1,2-Cyclohexanediol, 1460-57-7; *trans*-1,3-cyclohexanediol, 5515-64-0; *tert*-butylethylene, 558-37-2; *tert*-butylethylene oxide, 2245-30-9; ethyl 1-methyl-2-oxocyclohexanecarboxylate, 5453-94-1; *trans*-2-(hydroxymethyl)-2-methylcyclohexanol diacetate, 69551-51-5; 1-bromo-1-methylcyclohexane, 931-77-1; 1-methylcyclohexanol, 590-67-0; jesromotetrol acetate, 69551-52-6.

References and Notes

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