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THE NMR SPECTRA AND CONFIGURATIONS OF SOME 2,5,5-TRISUBSTITUTED 1,3-DIOXANS

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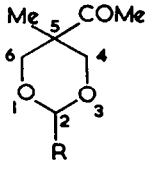
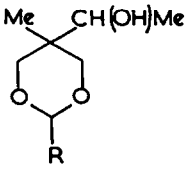
Abstract—The *cis* and *trans* isomers of some 2-substituted 5-acetyl-5-methyl-1,3-dioxans and of the corresponding 5-(α-hydroxyethyl) 5-methyl-1,3-dioxans have been prepared and their configurations assigned from a study of their NMR spectra and from H-bonding studies by IR.

IN A previous paper[1] the NMR spectra of 5-acetyl-5-methyl-1, 3-dioxan (I, R = H) and of the corresponding alcohol (II, R = H) were described. In order to investigate the positions of conformational equilibria in these compounds and to study the interesting features of their NMR spectra in more detail it was decided to prepare the anancomeric[2] relatives I and II (R = Me, t-Bu, Ph). 3-Keto-2-hydroxymethyl-2-methyl butanol, prepared from methyl ethyl ketone and formaldehyde[3] was reacted with the appropriate aldehyde and the resultant mixture of the *cis* and *trans* isomers of I was then separated. In the case of I (R = Me) this was achieved by preparative GLC whereas for I (R = t-Bu) fractional recrystallization was effective. Only one isomer of I (R = Ph) could be obtained, identical in m.p. with a compound previously prepared by Morgan and Griffiths.[4]

The epimerically pure ketones (I) were then reduced with LAH to give the corresponding alcohols (II).



I

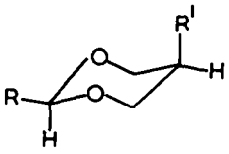


II

Since it has been shown[5] that *cis*-2-alkyl-5-t-butyl-1,3-dioxans exist largely in the chair conformation III (R^1 = t-Bu) with the bulky t-Bu group axial it is reasonable to expect the *trans* and *cis** isomers of I to exist predominantly in the conformations IV and V with the C2 substituent equatorial in both cases. A comparative study of the chemical shift data obtained on these compounds with similar data on alkyl substituted 1,3-dioxans supports the stereochemical assignments shown in Table 1. Thus

* In this paper *cis* and *trans* refers to the orientation of the C2 substituent with respect to the C5-Me group.

in the series of 1,3-dioxans III (R^1 = H,R = Me), III (R^1 = H,R = t-Bu), III (R^1 = H,R = Ph), the τ values of the C2 axial protons are 5·47, 6·01, 4·65 respectively[6] very close to those of the corresponding protons in IV (R = Me, t-Bu and Ph) and in V(R = t-Bu). The C2 axial proton in V (R = Me) absorbs at 0·11 ppm to higher field than in IV (R = Me) and a similar difference in chemical shifts has been observed between III (R^1 = t-Bu, R = Me) and its diequatorially substituted isomer. No appreciable



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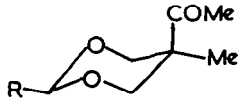

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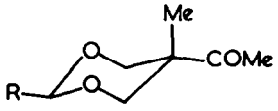
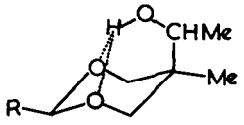
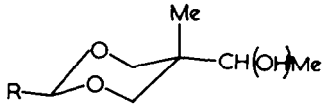


V



VI



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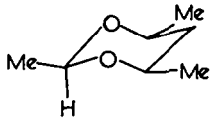
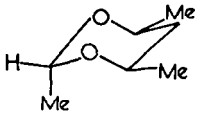
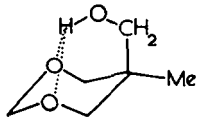


VIII



IX



X

amounts of C2 axially substituted forms can be in equilibrium with the conformations IV and V since equatorial C2 protons in 1,3- dioxans absorb[7,8] ca. 0·3–0·4 ppm to lower field than their axial counterparts. The chemical shift (8·81 τ) of the Me protons in III (R^1 = H,R = Me) and that (9·16 τ) of the t-Bu protons in III (R^1 = H,R =

t-Bu) is also similar to the corresponding shifts in IV (R = Me and t-Bu) and V(R = t-Bu) but in V(R = Me) the Me protons absorb at 8·76 τ. This latter observation might possibly suggest the presence of a small percentage of the C2 axially substituted conformation in equilibrium with V (R = Me) since in VIII[6] and IX the Me protons absorb at 8·81 τ and 8·68 τ respectively. However, this possibility is readily dismissed by comparing the chemical shifts of the C2 protons (5·46 τ in VIII and 4·87 τ in IX) with the value of 5·55 τ observed for V (R = Me). The weight of evidence is therefore in favour of an equatorial C2 substituent in all the compounds I and it is now left to determine the relative configuration at C5.

In each pair of isomers there is a difference of ca. 0·6 ppm between the chemical shifts of the C5 Me protons. Current chemical shift data[9] on Me absorptions in heterocyclic systems show that axial Me groups absorb at lower field than their equatorial counterparts and assuming this to be true for the systems under discussion the assignment of the configurations shown in Table 1 can be made. In addition, in the isomers assigned configuration IV the axial C4 and C6 protons absorb at ca. 0·4 ppm to higher field than in V consistent with the known[10] shielding of an axial proton by a vicinal equatorial Me group. An axial Me group deshields[11] a vicinal axial proton by ca. 0·20 ppm. An assignment of configurations at C5 based solely on these considerations is of course open to objection because the influence of the C5 acetyl group on the chemical shifts of the C4 (C6) protons and on the C5 Me protons has been ignored. The uncertainties in the detailed conformation of IV and V as well as in the anisotropic effect[12] of the acetyl group do not permit unequivocal assignment of C5 configurations to IV and V and to provide evidence of a different nature each ketone (I) was converted to its corresponding alcohol (II).

The H2 and C5 Me resonances in the NMR spectra (Table 2) of the alcohols VI and VII (derived from IV and V respectively) were in agreement with the structures shown with the C2 substituent equatorially orientated and the C5 Me equatorial in VI and axial in VII. An examination of the IR spectra (Table 3) of dilute solutions of the alcohols in carbon tetrachloride provided clear evidence in support of our stereochemical assignments. In 0·0005M solutions the isomers VIII showed a single sharp absorption at ca. 3630 cm^{-1} indicative of free OH whereas their isomers VI showed free OH and H-bonded OH frequencies which at this dilution can only be due to intramolecular H-bonding. Thus the compounds showing intramolecular H-bonding must be the *trans* isomers VI since only in VI can such a bond be formed with the ring O atoms. 5-Hydroxymethyl-5-methyl-1,3-dioxan has been shown[13] to prefer the conformation X. It may be seen from Tables 1 and 2 that the chemical shifts of the compounds I and II (R = H) are intermediate in value between those of the *cis* and *trans* anancomeric dioxans showing each of them to exist at room temperature as an equilibrium mixture of the two possible chair conformations.

Perhaps the most significant feature of the NMR spectra of II is the long range coupling of 3·0 to 3·2 Hz in the isomers VI and of 2 to 2·5 Hz in the isomers VII. A four bond coupling of 2·5 Hz has been observed[14] in certain 1,3-dioxans and the electronegativity of the O atoms has been suggested as a reason for these high values. The change in ^4J on going from VI to VII is accompanied by an increase in the C4 and C6 geminal coupling constant from −11·4 to −10·8 Hz. It is reasonable to attribute both this decrease in $|^4J|$ and increase in ^2J to the presence or absence of the intramolecular H-bond since in the case of ^2J it has been shown[15] that H-bonding involving

the oxygen lone pairs causes ^2J to become more negative by decreasing the hyperconjugative contribution. Further work is in progress on long range coupling in heterocyclic systems.

TABLE 1. NMR SPECTRA OF 2-SUBSTITUTED-5-ACETYL-5-METHYL-1,3-DIOXANS

Compound	Chemical shifts (τ)						Coupling constant (Hz)
	H2ax	H4eq,H6eq	H4ax,H6ax	*Me*CO	C2R	C5Me	J_{4ax4eq}
I (R = H)	5·34	5·84	6·51	7·80	—	9·05	−11·5
IV (R = Me)	5·44	5·68	6·62	7·75	8·81 (Me)	9·24	−11·9
V (R = Me)	5·55	6·28	6·28	8·02	8·76 (Me)	8·63	singlet
IV (R = t-Bu)	5·98	6·63	6·66	7·77	9·17 (t-Bu)	9·23	−11·5
V (R = t-Bu)	6·07	6·20	6·20	7·99	9·11 (t-Bu)	8·61	singlet
IV (R = Ph)	4·62	5·49	6·44	7·69	2·68 (Ph)	9·17	−11·9

TABLE 3. IR SPECTRAL DATA (cm^{-1}) (OH STRETCHING RGION) FOR THE *cis* AND *trans* ALCOHOLS (II)

Compound	Concentration	Free OH	H-bonded OH
VI (R = Me)	0·1M	3639	3495
	0·0005M	3638	3557
VII (R = Me)	0·1M	3639	3500
	0·0005M	3637	—
VI (R = t-Bu)	0·1M	3638	3500
	0·0005M	3637	3560
VII (R = t-Bu)	0·1M	3638	3505
	0·0005M	3634	—
VI (R = Ph)	0·1M	3638	3490
	0·0005M	3490	3560

EXPERIMENTAL

Elemental analyses were carried out by Dr. F. Pascher and E. Pascher, Micro-Analytical Laboratory, Bonn, Germany. M.ps are uncorrected. IR spectra were recorded on a Perkin Elmer 457 grating instrument as solns in CCl_4. 0·1M solns were measured in 0·5 mm cells and 0·0005M solns in 10 cm cells. NMR spectra were recorded on a Perkin Elmer R10 spectrometer and a Jeol 100 MHz spectrometer as 10% solns in CCl_4 or benzene with TMS as internal reference.

5-Acetyl-2,5-dimethyl 1,3-dioxan

3-Keto-3-hydroxymethyl-2-methyl butanol (13·2 g), prepared according to the method of Morgan and Griffith, was dissolved in benzene (100 ml), and allowed to stand at room temp for 1 hr in the presence of acetaldehyde (8·8 g) and a catalytic amount of *p*-toluene sulphonic acid. The soln was refluxed on a Dean and Stark water separator until the theoretical amount of water had separated. Excess benzene was removed *in vacuo* and the crude product distilled b.p., 91–93°/14 mm as a colourless mobile oil (12·6 g, 80%).

Separation of the diastereoisomeric mixture was achieved on an Aerograph autoprep gas–liquid chromatograph using a 20% carbowax column and H_2 carrier gas. The first isomer off the column was *trans*-5-acetyl-2,5-dimethyl-1,3-dioxan and was obtained as a colourless mobile oil b.p., 92–93°/16 mm, $n_D^{18·0}$ 1·4392. (Found: C, 60·63; H, 8·96; $C_8H_{14}O_3$ requires: C, 60·74; H, 8·92%). *cis*-5-Acetyl-2,5-dimethyl 1,3-dioxan was the second isomer off the column as a colourless mobile oil b.p., 97–98°/17 mm, $n_D^{18·0}$ 1·4439. (Found: C, 60·85; H, 9·01. $C_8H_{14}O_3$ requires: C, 60·74; H, 8·92%).

TABLE 2. NMR SPECTRA (BENZENE SOLUTION) OF CIS AND TRANS ALCOHOLS (II)

Compound	Chemical shifts (τ)									Coupling constants (Hz)		
	H2ax	H4eq	H4ax	H6eq	H6ax	C2Me	C5Me	MeCHOH	MeCHOH	J_{4eq4ax}	J_{6eq4ax}	J_{4eq6eq}
II (R = H)	5·38	6·46	6·76	6·07	6·59	—	9·28		9·01	− 11·2		1·4
VI (R = Me)	5·52	6·23	6·85	5·68	6·89	8·69	9·51	6·62	8·84	− 11·8	− 11·5	3·2
VII (R = Me)	5·53	6·51	6·51	6·02	6·42	8·64	8·79	6·76	9·15	singlet	− 10·75	2·0
VI (R = t-Bu)	6·06	6·25	6·90	5·74	6·95	—	9·64	ca 5·75	8·95	− 11·9	− 11·3	3·1
VII (R = t-Bu)	6·02	6·59	6·59	6·05	6·55	—	8·87	6·98	9·35	singlet	− 10·8	2·5
VI (R = Ph)	4·67	6·16	6·78	5·61	6·82	—	9·59	ca 5·60	8·95	− 11·9	− 10·4	3·0

5-Acetyl-5-methyl-2-t-butyl-1,3-dioxan

3-Keto-2-hydroxymethyl-2-methyl butanol (13·2 g) was refluxed in benzene (100 ml) with pivaldehyde (10·2 g) and a trace of *p*-toluene sulphonic acid as above. When the theoretical amount of water had separated excess benzene was removed *in vacuo* and the crude product was charcoaled and recrystallized from 30–40° light petrol. The first isomer to crystallize was *cis*-5-acetyl-5-methyl-2-t-butyl-1,3-dioxan (9·9 g) either as needles or plates m.p., 87–88° depending on the concentration of the soln. (Found: C, 66·08; H, 9·97. $C_{11}H_{20}O_3$ requires: C, 65·97; H, 10·07%). When no more crystals could be obtained the mother liquors were evaporated to dryness to give a white solid (2·4 g) in which the second isomer was concentrated. Separation was achieved by passing the mixture (2·4 g) down a Grade 1 neutral Woelm alumina column (225 g) in 40–60° light petrol. *trans*-5-Acetyl-5-methyl-2-t-butyl-1,3-dioxan (0·35 g) was the second isomer off the column as white needles m.p., 55–57° from 40–60° light petrol. (Found: C, 66·04; H, 9·74; $C_{11}H_{20}O_3$ requires: C, 65·97; H, 10·07%).

5-Acetyl-5-methyl-2-phenyl-1,3-dioxan

3-Keto-2-hydroxymethyl-2-methyl butanol (13·2 g) in benzene (100 ml) was refluxed as above with benzaldehyde (12·2 g) and a trace of *p*-toluenesulphonic acid. When the reaction was complete excess benzene was removed *in vacuo* and the crude product was recrystallized from diethyl ether to give *cis*-5-acetyl-5-methyl-2-phenyl-1,3-dioxan (19·1 g) as white needles m.p., 102–103°. (Found: C, 71·40; H, 7·26; $C_{13}H_{16}O_3$ requires: C, 70·89; H, 7·32%). This compound was also isolated by Morgan and Griffith[4] as a white solid m.p. 103°. Evaporation of the mother liquors gave a mixture of isomers which NMR spectroscopy showed contained only trace amounts of *trans*-5-acetyl-5-methyl-2-phenyl-1,3-dioxan.

Preparation of 5-(α-hydroxyethyl)-5-methyl-2-substituted-1,3-dioxans

General procedure. The 5-acetyl-5-methyl-2-substituted-1,3-dioxan was dissolved in Na-dry ether (150 ml) and added to a stirred mixture of LAH in Na-dry ether. After addition the reaction was refluxed on a water bath for 2 hr, excess LAH was destroyed by the addition of wet ether and finally water, the ether layer was dried (Na_2SO_4) and concentrated and the crude product distilled or recrystallized.

cis-5-(α-*Hydroxyethyl*)-2,5-*dimethyl*-1,3-dioxan (1·6 g, 78%) was obtained from *cis*-5-acetyl-2,5-dimethyl-1,3-dioxan (2 g) as a colourless mobile oil b.p., 115–116°/20 mm $n_D^{20°}$ 1·4538. (Found: C, 60·18; H, 10·06; $C_8H_{16}O_3$ requires: C, 59·98; H, 10·07%).

trans-5-(α-*Hydroxylethyl*)-2,5-dimethyl-1,3-dioxan (1·8 g, 80%) was obtained from *trans*-5-acetyl-2,5-dimethyl-1,3-dioxan (2·2 g) as a colourless mobile oil b.p. 117–119°/15 mm $n_D^{20°}$ 1·4561. (Found: C, 59·77; H, 10·03; $C_8H_{16}O_3$ requires: C, 59·98; H, 10·07%).

cis-5-(α-*Hydroxyethyl*)-5-*methyl*-2-*t-butyl*-1,3-dioxan (3·4 g, 77%) was obtained from *cis*-5-acetyl-5-methyl-2-t-butyl-1,3-dioxan (4·5 g) as white felted needles from 30–40° light petrol m.p., 79–80°. (Found: 65·21; H, 10·93; $C_{11}H_{22}O_3$ requires: C, 65·31; H, 10·96%).

trans-5-(α-*Hydroxyethyl*(-5-*methyl*-2-*t-butyl*-1,3-*dioxan* (0·175 g, 57%) was obtained from *trans*-5-acetyl-5-methyl-2-t-butyl-1,3-dioxan (0·3 g) as white needles m.p., 74–76° from 30–40° light petrol.

cis-5-(α-*Hydroxyethyl*)-5-*methyl*-2-*phenyl*-1,3-*dioxan* (4·5 g, 74%) was obtained from *cis*-5-acetyl-5-methyl-2-phenyl-1,3-dioxan (6·0 g) as white needles m.p., 67–68° from 30–40° light petrol. (Found: C, 70·29; H, 8·21; $C_{13}H_{18}O_3$ requires: C, 70·24; H, 8·16%).

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