The Stereochemistry of Caucalol diacetate

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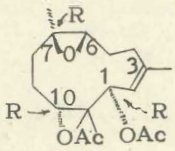
The stereochemistry of caucalol diacetate, which extracted from Torillis scabra D.C. is determined on the basis of the modified benzoate rule and NMR ring current due to the epoxide ring.

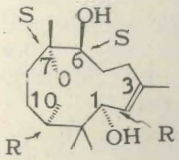
Introduction

Torillis scabra D.C. is pernnial herbs, which is distributed from Japan to Taiwan. The fluffy seeds are ultilized as astritive antiphogistics. Caucalol diacetate, $C_{19}H_{30}O_5$, is isolated from the seeds of Torillis scabra D.C. in 0.21% yield together with apocaucalol (epicaucalol) diacetate, $C_{19}H_{30}O_5$, a minor component, the yield of which is 0.014%.[1]

The planar structure was assigned[2] to caucalol diacetate, which can be hydrolyzed with base to the 10-monoacetate, but further hydrolysis is accompanied by a rearrangement leading to an isomer, isocaucalol, which in acetylation yields the straightforward isocaucalol diacetate. The stereochemistry[3] of caucalol diacetate and isocaucalol are shown in Fig. 1 were proposed on the basis of Brewster's[4] and Mill's rules[5] and the NMR ring current due to the epoxide.



Caucalol diacetate



Isocaucalol

Fig. 1

Caucalol does not exist as the free diol but as diacetate in the plant, and upon hydrolysis is readily converted to isocaucalol, so that only a few experiments have been carried out on the derivatives having the intact caucalol skeleton. The stereochemistry of caucalol is mainly derived from isocaucalol.[3] Also it should noted that the Benzoate rule and Mill's rule which had been applied in former studies[3] have limits in their application. Namely, applications of Benzoate rule and Mill's are restricted, respectively, to secondary alcohols having two groups L and S of similar polarizability, or to secondary alcohols having substituents MP and LP (less polar) with similar steric requirements.

These reqirements are not fulfilled at the allylic C_1-OH of isocaucalol, Fig. 2, and therefore it is doubtful whether these rule can be applied at all.

For this reason, in this studies, newly modified benzoate rule[6] has been applied to determine the configurations of caucalol diacetate at C_1 and C_{10}. Furthermore free caucalol is first time obtained from caucalol diacetate with careful $LiAlH_4$ reduction. So the stereochemistry of caucalol diacetate can directly derived from caucalol. The obtained results shown in Fig. 3, are exactly antipodal to those reported previously[3] (Fig. 1).

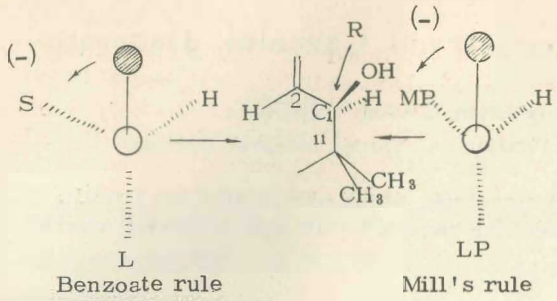


Fig. 2

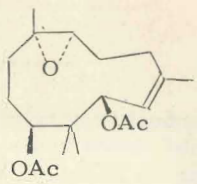


Fig. 3

Experimental Section

Caucalol:

Lithium aluminum hydride(120 mg) was slowly added to a solution of caucalol diacetate (400 mg) in dry tetrahydrofuran(4 ml), the solution was kept for 10 minutes at room temperature and then treated with ethyl acetate(2 ml) to decompose the excess of lithium aluminum hydride. The reaction mixture was evaporated in vacuo to give a solid mass. After extraction with ether the solvent was removed to afford crude caucalol. Recrystallization from benzene gave prisms, m.p. 180–181°, yield 200 mg.

Calcd. for $C_{15}H_{26}O_3$: C, 70.81 ; H, 10.31%(found: C, 70.95; H, 10.18%)
IR(KBr): 3350(OH), 1670 and 870 cm^{-1} (c=c)
NMR($CDCl_3$): 0.91(s, C_{11}-Me), 1.0(s, C_{11}-Me), 1.32(s, C_7-Me), 1.8(s, C_8-Me), 3.22(m, C_{10}-H), 4.16(d, J 11, C_1-H), 5.4 ppm(q, J 1, 11, C_2-H)
$[\alpha]_D = +41.2°$ (c=1.0, $CHCl_3$)
MS: 254(M, 1.5%), 236(M–18, 10%), 218(M–36, 3%), 127(M–127, 3%), 109(M–145, 80%), 43(CO , 100%).

A solution of caucalol(50 mg) in pyridine(0.6 ml) and acetic anhydride(0.5 ml) was kept at room temperature overnight, and the mixture was poured into ice water with rapid stirring. The white precipitate was recrystallized from n-hexane to afford caucalol diacetate as prisms, m.p. 120–121°, yield 35 mg. The IR spectra of the crystals were identical with that of authentic caucalol diacetate. Also there was no melting point depression when mixed with an authentic sample.

Benzoylation of caucalol:

A solution of benzoyl chloride(1.3 g) in benzene(20 ml) was added to a cooled solution of caucalol(2 g) in pyridine(20 ml) and the solution was allowed to stand in ice box for 3 hours. Ice water was added to the reaction mixture, then extracted with ether. The combined ether extract was washed with water, evaporated to dryness, chromatographed on silica gel(120g, Merck) and eluted with benzene/ethyl acetate(1:1). The elution from the first band was recrystallized from n-hexane/ether(1:1) to afford prisms, caucalol dibenzoate, m.p. 187–188°, yield 300 mg; the second elute was recrystallized from the same solvent to afford prisms, isocaucalol-1-benzoate, m.p. 172–173°, yield 180 mg, confirmed by mixed melting point test, IR and NMR spectra. The third elute was recrystallized from n-hexane/ether(1:1) to afford needles, caucalol-1-benzoate, m.p. 189–190°, yield 520 mg.

Caucalol dibenzoate;
Calcd. for $C_{29}H_{34}O_5$: C, 75.30 ; H, 7.41% (found: C, 75.27 ; H, 7.47%)
IR(KBr): 1714 and 1275(benzoate), 1603, 1583, 1453 and 720 cm^{-1} (phenyl)
NMR($CDCl_3$): 1.06(br.s, C_{11}-Me), 1.45(s, C_7-Me), 1.93(s, C_8-Me), 3.15(q, J 10.5, 4.0, C_6-H), 5.22(m, C_{10}-H), 5.44 ppm(q, J 1, 11, C_2-H)

Caucalol-1-benzoate;
Calcd. for $C_{22}H_{30}O_4$; C, 73.71 ; H, 8.44%(found: C, 73.62 ; H, 8.49%)
IR(KBr): 3700 and 3500(OH), 1603, 1583, 1453 and 703 cm^{-1}(phenyl)
NMR($CDCl_3$): 0.9(s, C_{11}-Me), 1.22(s, C_{11}-Me), 1.42(s, C_7-Me), 1.82(s, C_3-Me), 2.78(q, J 3, 11, C_6-H), 3.38(q, J 2, 7, C_{10}-H), 5.37(q, J 1, 11, C_2-H), 5.69(d, J 11, C_1-H), 7.3 - 8.2 ppm(m, phenyl)
ORD(methanol): cell length 1 cm. c=0.0198 mg/ml, room temp.

$$[\phi]^{tr}_{240} = -16{,}000^0 , [\phi]^{pk}_{215} = +24{,}000^0$$

Isocaucalol-1-benzoate ketone

A chromium-pyridine complex solution prepared from 5 ml of pyridine and 80 mg of chromium trioxide was added to a soulation of 130 mg of isocaucalol-1-benzoate in 3 ml of pyridine at 0°C. The reaction mixture was stirred at 0°C for 5 hours, and left at room temperature for 5 days. The mixture was treated with water, and extracted with ether. The extract was washed with water and evaporated to yield a pale brown oil. The oil was chromatographed on silica gel(6 g, Merck) and eluted with benzene/ethyl acetate(1:1). The elution from the first band was recrystallized from n-hexane to give prisms, isocaucalol-1-benzoate ketone, m.p. 163-164°.

Calcd. for $C_{22}H_{28}O_4$: C, 74.13 ; H, 7.92%(found: C, 74.24 ; H, 7.76%)
IR(KBr): 1707(ketone, benzoate), 1270(benzoate), 1603, 1580, 1450 and 710 cm^{-1} (phenyl)
NMR($CDCl_3$): 1.1(s, C_{11}-Me), 1.23(s, C_{11}-Me), 1.26(s, C_7-Me), 1.73(d, J 1, C_3-Me), 2.2(m, C_5-H_2), 3.92(m, C_{10}-H), 5.24(q, J 1, 11, C_2-H), 6.06(d J 11, C_1-H), 7.34-8.09 ppm (m, phenyl)
ORD(methanol): cell length 1 cm, c=0.018 mg/ml, room temp.

$$[\phi]^{tr}_{240} = -9{,}000^0 , [\phi]^{pk}_{217} = +20{,}000^0$$

Caucalol-10-benzoate:

Caucalol dibenzoate(200 mg) was treated with 3% alcoholic potassium hydroxide solution(5 ml) for 18 hours at room temperature. Ice water was added to the reaction mixture, which was then extracted with ether.

The combined ether extract was washed with water, evaporated to dryness, chromatographed on silica gel(15 g, Merck) and eluted with benzene/ethyl acetate(1:1) to afford crystalline fractions which were recrystallized from n-hexane to give prisms, m.p. 199-200°, yield 80 mg.

Calcd. for $C_{22}H_{30}O_4$: C, 73.71:H, 8.44%(found: C, 73.75:H, 8.51%)
IR(KBr): 3500(OH), 1710 and 1270(benzoate), 705 cm^{-1} (phenyl)
NMR($CDCl_3$): 0.90(s, C_{11}-Me), 1.1(s, C_{11}-Me), 1.32(s, C_7-Me), 1.89(br. s, C_3-Me), 3.12(q, J 3, 10, C_6-H), 4.25(d, J 11, C_1-H), 5.45(q, J 11, 1 C_2-H), 5.09(m, C_{10}-H), 7.37-8.08 ppm(m, phenyl)
ORD(methanol): cell length 1 cm, c=0.026 mg/ml, room temp.

$$[\phi]^{pk}_{232} = +6{,}200^0 , [\phi]^{tr}_{215} = -4{,}100^0$$

Instruments used :

The spectra were measured with the following instruments:
UV, Beckman DK-2 and HITACHI EP-2; IR, Hitachi EPI-S2 ;
NMR, Varian A-60, HR-100 ; ORD, JASCO ORD/UV-5 ; MS, Hitachi RMV-6D.

Results and Discussion

Modified benzoate rule (benzoate sector rule) [6]:

In the Brewster's benzoate rule [4], the stereochemistry of a carbinol having the absolute configuration such as 1 (Fig. 4) is considered, in which S and L represent a group with the small and larger steric requirement, respectively, but having similan polarizabilities. The secondary alcohol shown in 1 can take three conformational struc-

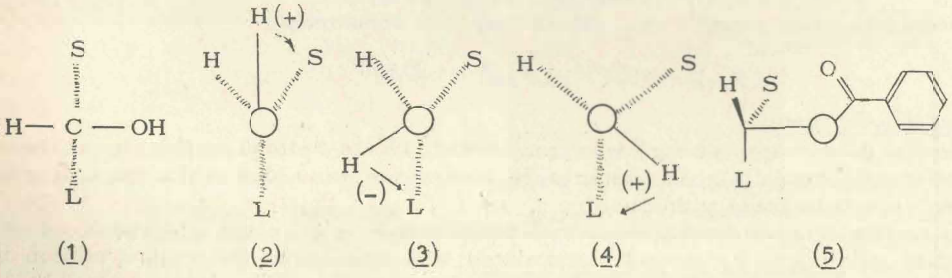
tures 2, 3, and 4 when projected through the axis of the C-O bond. A more bulky group, such as the benzoate, on the other hand, is not freely rotating and will tend to be flanked by the two smallest substituents. When the secondary alcohol 1 is converted into its benzoate, it will tend to assume the conformation 2 or 5 and thus the molecular rotation difference($[\phi]_D$ = $[\phi]_D$ bemzoate - $[\phi]_D$ carbinol) between the benzoate and the carbinol would be positive, since the group S is more polarizable than the hydrogen atom.

According to Mills' rule[5] on the other hand, the rotational shift of an alcohol having the absolute configuration 6, in which MP(more polarizable group) and LP (less polarizable group) are the groups with the same steric requirement but with different polarizabilities, should be positive. This is based on the assumption that the population of the conformer 7 is equal to that of conformer 8, so that the direction of the shift is governed by the larger rotatory contribution of the unit 7 which is positive.

The application of the benzoate rule or the Mills' rule at the allylic C1-OH of isocaucalol and its derivatives is illustrated in Fig. 2, and both rule indicate the configuration to be R[3].

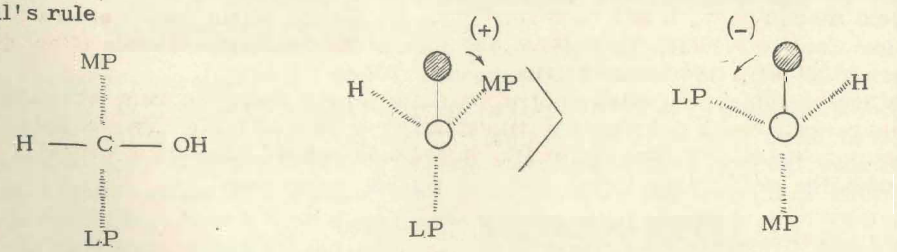
But, applications of the benzoate and Mills' rule are restrictively, to secondary alcohols having two groups of similar polarizabilities, or with similar steric requirements (Mill's rule). These requirements are not fulfilled at the allylic C1-OH of isocaucalol, Fig. 2. In the case of menth-4-en-3β-ol, Fig. 5, for example, it is not feasible to predict whether the shift is going to be determined by the positive rotation of conformer 9 favored on the grounds of bulkiness(benzoate rule) or the negative rotation of conformer 10 having the larger polarizability (Mills' rule).

Benzoate rule



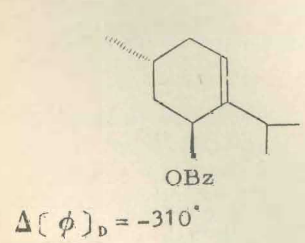
(1) (2) (3) (4) (5)

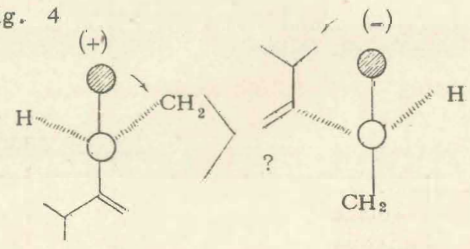
Mill's rule



(6) (7) (8)

Fig. 4





(9) (10) (11)

Fig. 5

These results mean that it is not sufficient to consider only the steric or polarizability effects of the β-carbons as Brewster did. In the benzoate rule, a benzoyloxy group is considered to have only one plane of symmetry, viz., the plane of the benzene ring. This division of the two sectors, sometimes, is not sufficient as described above, and therefore further symmetric properties are assigned. If it is assumed that the two oxygens of the carboxyl group has the same electric structures, there is another plane of symmetry which is perpendicular to the plane of the benzene ring. When a benzoate is viewed from the phenyl ring towards the carboxyl group (Fig. 6), the space can be divided into four sections by plane of symmetry. These four sectors are further dissected by planes running through, the two oxygen atoms as indicated in Fig. 7, when the benzoate is viewed as in Fig. 6. The bonds situated in the shaded and unshaded sectors will make positive and negative contribution, respectively. In this case, as Brewster considerded, the benzoyl group is flanked by the hydrogen and the smaller group. It is considered that α, β and β, r-bonds play dominant roles in determining the rotation, and that the rotatory contribution of a double bond would be larger than that of a single bond.

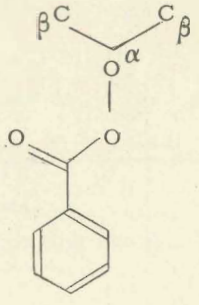


Fig. 6

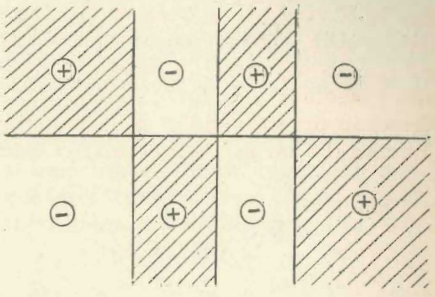


Fig. 7

Namely, the rotatory power of the compound would be decided by the sign of the sector having a double bond. In Brewster's benzoate rule, the discussion regarding optical rotation were based solely on the sign of the molecular rotation difference at the D-line (589 mμ). However, it was noticed that benzoates have a Cotton effect at about 230 mμ (ε= 14,000) and that its sign is in accordance with that of the molecular rotation difference. Thus, in the sector rule, the Cotton effect of the benzoate at 230 mμ (a=100~300) is measured; furthermore, it has been fond that the Cotton effect due to saturated ketones (290±20 mμ, a=5~250) does not affect the sign of the benzoate Cotton effect due to the relatively small amplitude of the former.

This sector rule incorporates Brewster's extended benzoate rule and therefore is more general and can be extended further to cases in which his rule was not applicable. This sector rule has now been applied to determine the configuration of caucalol diacetate at C_1 and C_{10}.

Configuration at C :

Caucalol diacetate is an 11 membered ring sesquiterpenoid and can adopt many conformation according to Dreiding models. However, the NMR coupling constants, $J_{1,2}$, $J_{5,6}$ and $J_{9,10}$ of caucalol and its derivatives are almost constants as shown in Table 1. Thus indicates that these compounds all adopt the same preferred conformation.

TABLE 1. Coupling constants (cps, $CDCl_3$ of caucalol derivatives)

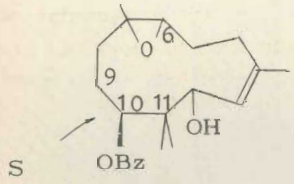
	$J_{1,2}$	$J_{5,6}$	$J_{9,10}$
Caucalol	11	3.5, 11	3.5, 5.5
Caucalol-10-actate	11	3 , 11	4.5, 5
Caucalol diacetate	11	3.6, 10.2	4.05, 5.5

Caucalol-1-benzoate	11	3, 11	2.0, 6.0
Caucalol-10-benzoate	11	3, 10	m*
Caucalol-10-acetate-1-benzoate	10	3.5, 10.9	4.0, 5.8
Caucalol dibenzoate	11	4, 10.5	m*

Remarks; * not clear

Application of the sector rule to the determination of the C_{10} configuration in caucalol-10-benzoate is rather simple. Because only α,β and β,γ -bonds contribute dominantly to the rotation, it could not be affected by the cis-trans nature of the epoxide and the double bond. The results are shown in Fig. 8. The β,γ -bonds in the positive and negative sectors compensate each other, so that only the contribution of the α, β bond need be considered. The observed rotational shift is positive, $[\phi]^{pk}_{234} = +6,200^0$, and this establishes C_{10} configuration as being S as shown in Fig. 8. In this case, application of Brewster's benzoate rule also lead the same conclusion, but in previous studies, the C_{10} configuration was derived on mechanistic grounds from the C_6 configuration of isocaucalol(which turned out to bo opposite from that deduced in the present studies) because a caucalol derivative having no substituents on C_{10} were unavailable at that time.

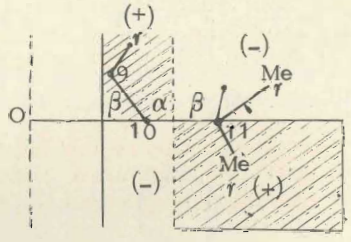
C_{10}-OH Configuration



Caucalol-10-benzoate

$[\phi]^{pk}_{232m\mu} = +6,200^0$

$[\phi]^{tr}_{215m\mu} = -4,100^0$



Benzoate sector (+)

Fig 8

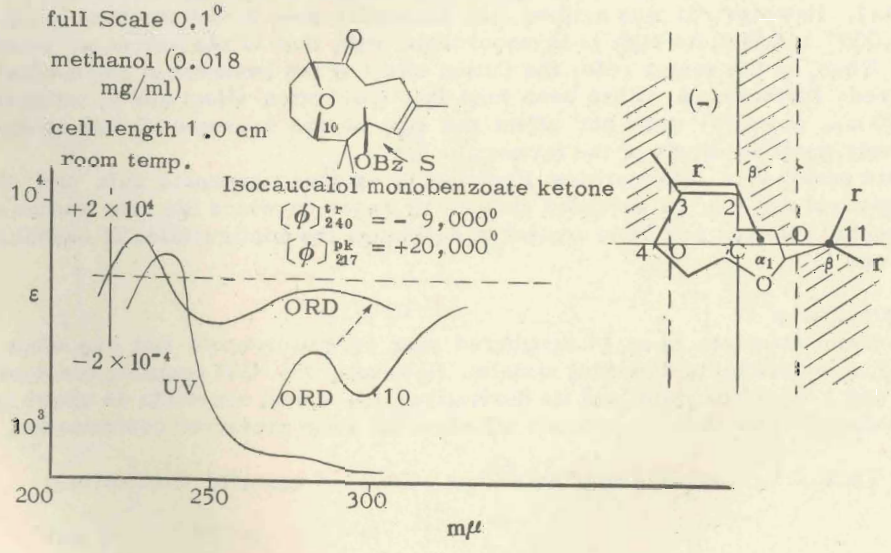


Fig. 9

Configuration at C_1:

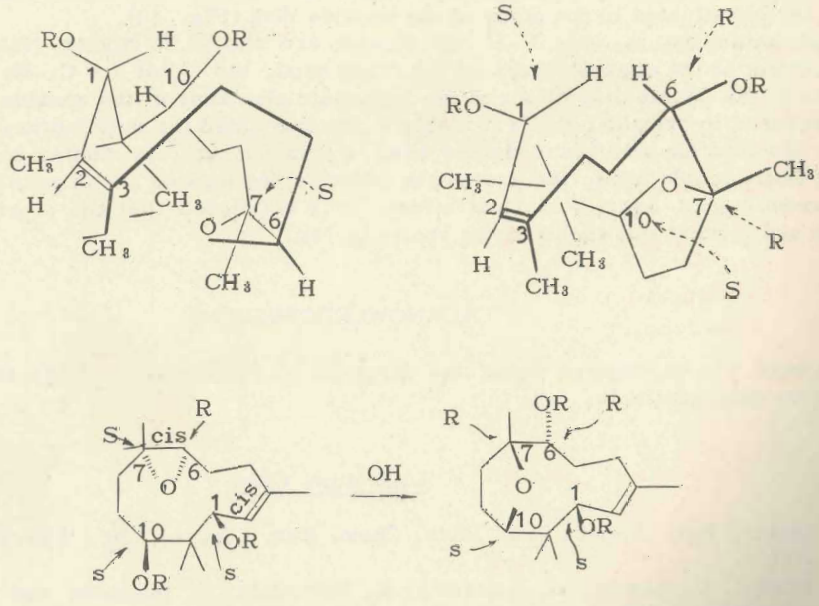
Application of the sector rule to isocaucalol-1-benzoate monoketone enable one to determine the C_1 configuration. The ORD curve and UV spectrum of its are shown in Fig. 9.

In this case, the Cotton effect of the benzoate at 240 mμ is negative and this establishes the C_1 configuration to be S as shown in Fig. 9. The amplitude of the Cotton effect(a) of ketone at 345 mμ, which appeared in a 10-fold concentrated solution, is much smaller than that due to the benzoate chromophore and it is obvious from Fig.9 that the former is too small to affect the sign of the latter. The configuration of C_1 in caucalol-1-benzoate and isocaucalol-1-benzoate also give the same results, i.e., an S-configuration. (Fig. 9)

Epoxide and Double Bond:

The anisotropic long-range shielding effect of a three-membered ring on neighbouring protons has been the subject of intensive studies. Particularly in bridged ring systems the NMR signal arising from the methylene-bridged proton anti to an exo-cyclopropane [7], -epoxide [8-12], and -aziridine ring [13] is significantly shifted upfield by this shielding effect. From the NMR study of bridged ring systems, K. Tori et al.[12] summarized that a proton situated above the plane of the ring is more shielded, whereas a proton located near the plane of the ring or in the neighborhood of the heteroatom in the ring is less shielded.

From a study of the coupling (Table I), $J_{1,2}$ $J_{5,6}$ and $J_{9,10}$ in caucalol and its derivatives and application of the relationship between these vicinal coupling constants and the dihedral angles [14) 15)], the preferred conformation between C_1-H, C_6-H, C_{10}-H and their neighbouring protons can be deduced, and these are depicted in Fig. 10.



caucalol (R=H) isocaucalol (R=H)

Fig. 10

By taking into account the configuration of C_1 s and C_{10} s and the cis-trans nature of the C_2-C_3 double bond and the epoxide, there are four possible structures, namly cis

epoxide/cis double bond, cis epoxide/trans double bond. However, structures having a trans epoxide can be rule out, since combination with neither a cis nor trans double bond gave conformation satisfying the requirements imposed by coupling constants and devoid of steric hindrance.

On the other hand, the cis epoxide, combined with either a cis or trans double bond fulfil requirements. The comparison of the chemical shift of caucalol, isocaucalol and their diacetate due to C_1-H, C_2-H, C_3-Me, and C_{11}-Me are shown in Table 2.

TABLE 2. Chemical shift of caucalol, isocaucalol and their diacetate, in $CDCl_3$, ppm from internal TMS

	C_1-H	C_2-H	C_3-Me	C_{11}-Me
Caucalol	4.16	5.4	1.80	1.0
Isocaucalol	4.41	5.18	1.74	1.21
Difference of above	-0.25	+0.22	+0.06	-0.21
Caucalol diacetate	5.46	5.24	1.88	0.92
Isocaucalol diacetate	5.70	5.13	1.73	1.06
Difference of above	-0.24	+0.11	+0.15	-0.16

The table shows that the C_1-H and C_{11}-Me protons in caucalol and its diacetate are shifted downfield, whereas the C_2-H and C_3-Me protons are shifted upfield when compared to the corresponding protons in isocaucalol and its diacetate.

This relation can only be satisfied by a caucalol having an α-cis epoxide and a cis double bond and the corresponding isocaucalol. The stereostructures of these molecules are depicted in Fig. 10. It is seen that C_1-H and C_{11}-Me are situated above but C_2-H and C_3-Me are situated in the plane of the epoxide ring (Fig. 10).

In this conformation, the C_1-H and C_{11}-Me are shifted to higher fields by the ring current effect of the epoxide ring; on the other band, the C_2-H and C_3-Me are shifted to lowfields by the deshielding effect of the long-pair electrons of the epoxide oxygen. Thus the differences in chemical shifts in Table 2 are accounted for satisfactory. In the combination of α-cis epoxide/trans double bond, β-cis epoxide/cis double bond or β-cis epoxide/trans double bond, the protons in question are located at the positions where the ring current cannot exert a marked effect. It is concluded that the stereochemistry of caucalol and isocaucalol should be as shown in Fig. 10.

ACKNOWLEDGEMENTS

The work was undertaken under the direction of Professor k. Nakanishi, to whom I express my deep gratitude.

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