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STUDIES ON JULIMYCINS—V

THE CONFIGURATIONS AND CONFORMATIONS OF JULICHROME $Q_{1\cdot3}$ AND ITS C_9-EPIMER

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Abstract—The hydrolysis of 9-O-acetyl derivative of julichrome $Q_{1\cdot3}$ (I) gave the C_9-epimer of I. The configuration of C_9-OH of I has been assigned as β by the comparison of the spectroscopic properties of I and its C_9-epimer. The conformations and intramolecular H-bonding aspects of both compounds are also discussed.

IN THE preceding paper,[1] the structure of julichrome $Q_{1\cdot3}$ was establishedas I, in which the configuration at C_9 remained unknown. Further experiments for the confirmation of the configuration are described in the present paper.

The determination of the configuration of C_9-OH was based on comparison of the physical and chemical properties of I with those of the corresponding C_9-epimer. Therefore, an attempt to prepare the epimer by solvolysis of the 9-O-acetate was made, taking advantage of the benzylic position.

The acetylation of I with acetic anhydride at room temperature gave various acetylation products depending on the conditions. The acetates, which were successfully purified by continuous development TLC[2] and characterized by IR and NMR, are shown in Chart 1.

Acetic anhydride in pyridine reacts predominantly on the phenolic OH groups and then on the benzylic OH group to give 8,8′,9-O-triacetate (II), which was hydrolysed to 8,9-O-diacetate (IV) during the purification by TLC on metal free silica gel. The acetylation of I in the presence of anhydrous sodium acetate gave 8-O-acetate (III) and then IV, but the peri OH group at $C_{8'}$, and the tertiary OH groups at C_3 and C_3' remained unaffected. While, the acetylation in the presence of *p*-toluenesulfonic acid for a few minutes gave 9-O-acetate (V) as a main product,* and the reaction for 1 hr afforded 3,3′,9-O-triacetate (VI), but the phenolic OH groups were unchanged. The correlations between the acetates are also shown in Chart 1.

In order to obtain the desirable C_9-epimer of I, V was treated with aqueous acetone. In this reaction, V gave two products in a ratio of 1 : 1 approximately. One product having the lower R_f value was easily identified as I by TLC and IR spectrum. The other product (VIII) was assumed to be the epimer from the IR spectrum closely resembled that of I. Since the bichromate oxidation of VIII gave julichrome $Q_{1\cdot4}$ (IX) as the same reaction of I,[1] it is obvious that VIII is the epimer of I at C_9. By the similar hydrolysis, VI, gave two products, X and XI, in almost equal amount, and the both

* In addition to V, 3′-O-acetate, 3,9-O-diacetate, 3′,9-O-diacetate and unchanged material was characterized.

CHART 1

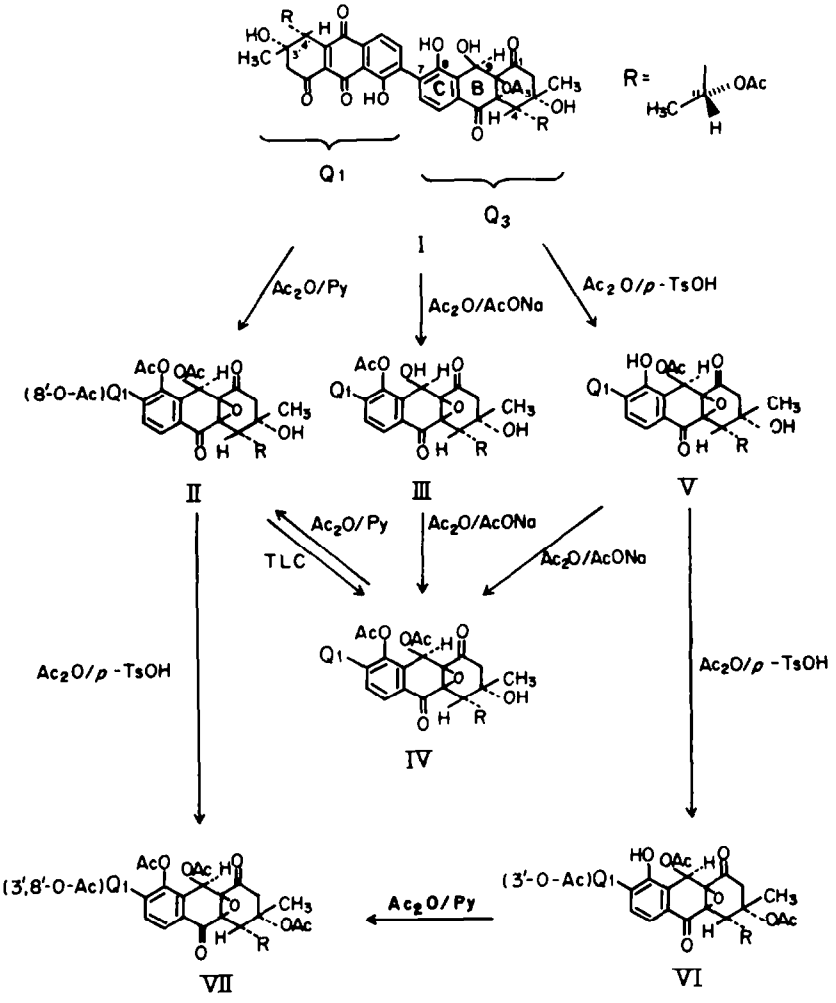
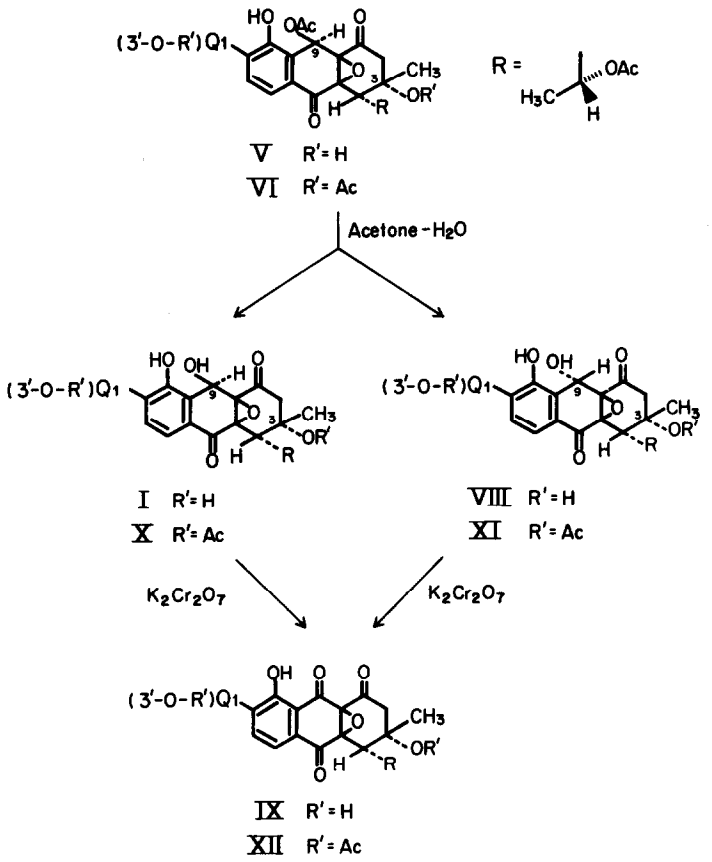

R =
Q1
Q3
I
Ac2O/Py
Ac2O/AcONa
Ac2O/p-TsOH
(8'-O-Ac)Q1
II
III
V
TLC
IV
(3',8'-O-Ac)Q1
VII
(3'-O-Ac)Q1
VI

CHART 2


(3'-O-R')Q1
HO
OAc
H
O
9
O
3
CH3
OR'
H
R
O
R =
H3C
OAc
H
V R'=H
VI R'=Ac
Acetone-H2O
OH
I R'=H
X R'=Ac
VIII R'=H
XI R'=Ac
K2Cr2O7
K2Cr2O7
IX R'=H
XII R'=Ac

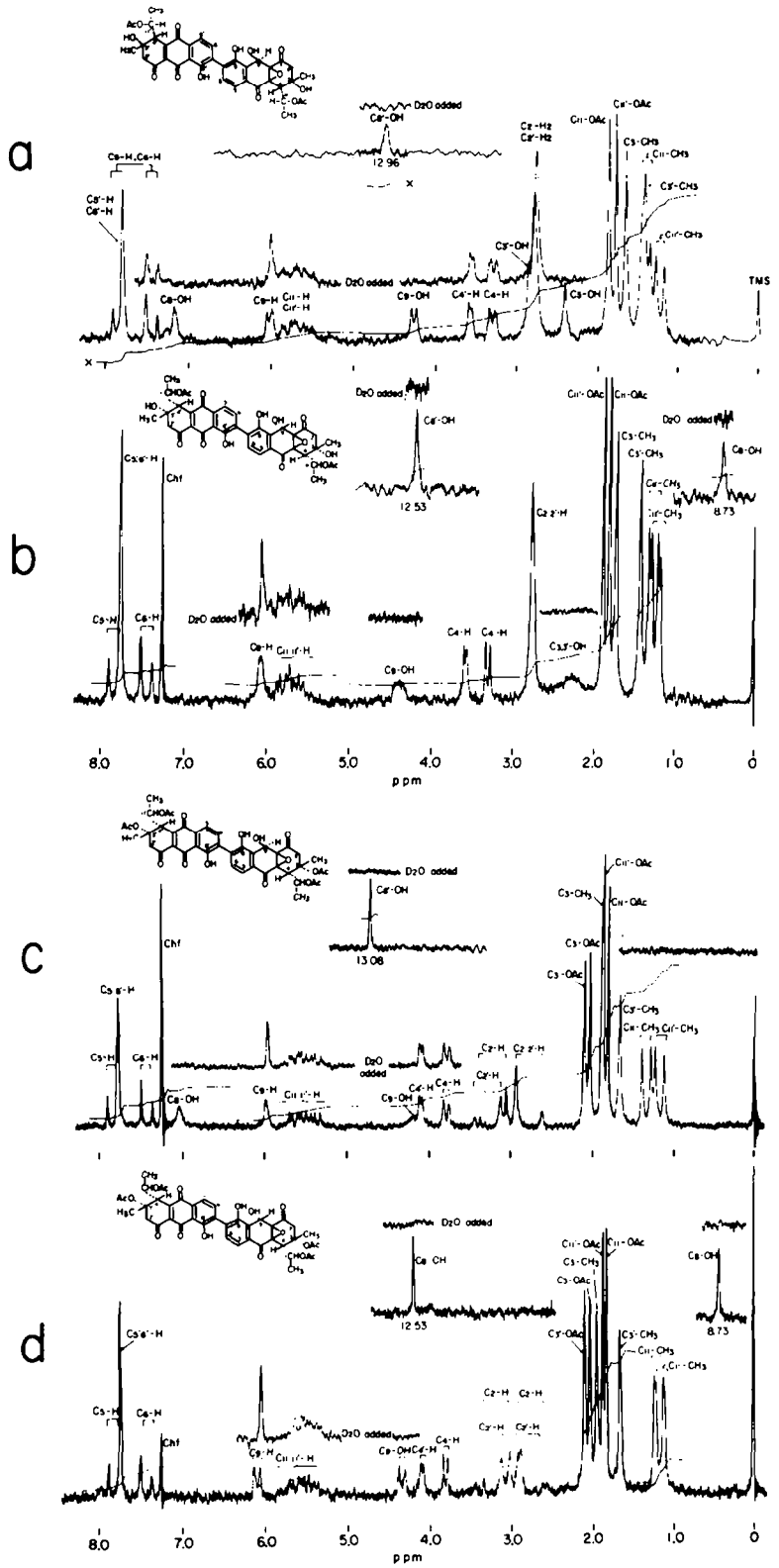

a
b
c
d
D2O added
12.96
12.53
13.08
8.73
TMS
ppm
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0

FIG. 1.

products were oxidized to the same compound XII, which was identical with the acetylation product of IX[1] (Cf. Chart 2). Therefore, X and XI are the isomers associated with the configuration at C_9, and X, which has the lower R_f value, is assigned as C_9-normal compound from the NMR spectrum close to that of I. As for 8,9-O-diacetyl compounds, the hydrolysis of the C_9-OAc group under the same conditions was unsuccessful, and the starting materials were recovered. Accordingly, the hydrolysis, presumably through the benzylic carbonium ion, would be accelerated by the C_8-OH function.

In order to infer the configuration at C_9, the NMR spectra* of the two couples of the epimers (I–VIII and X–XI) were compared (Cf. Fig. 1). However, it was not a simple matter to conclude the configuration from the comparison, and the spectra presented some complicated problems on the conformation of the respective molecules. First of all, the conformation of the A ring of Q_3 unit is discussed. The C_3-Me signals of both epimers, I and VIII, appear in a lower field than those of C_3'-Me (Q_1 unit) by about 0·3 ppm (Cf. Fig. 1a, b), as it was observed in compounds such as IX having Q_4 unit. Since the downfield shift of the C_3-Me signal is attributable to the epoxy group close to the Me group,[3] the C_3-Me group must be axial as C_3'-Me. Moreover, in both compounds the conformation of the C_4-sidechain is also the same with that of Q_1 unit[4] on account of the chemical shift of C_{11}-H and the coupling constant between C_4-H and C_{11}-H. Thus, the conformation of the A ring, in both epimers, is similar to that of Q_1 unit and reasonably explained by the partial structure shown

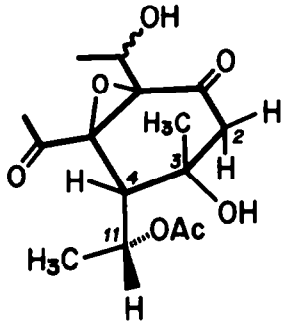


FIG. 2 The conformation of A ring.

in Fig. 2. The same conclusion is obtained from the NMR spectra of X and XI (Cf. Fig. 1c, d).

In the spectra of I and VIII, a considerable difference is observed in the chemical shifts of C_8-OH, $C_{8'}$-OH, C_9-OH and C_{11}-Me, but not in that of C_9-H. The behaviour of C_9-H and C_{11}-Me seems especially significant. Since the C_{11}-Me group is far from C_9, the shift of the C_{11}-Me signal is unlikely unless the conformation of the B ring has been transformed by the alternation of C_9-OH. As the C_{11}-Me group is orientated toward the CO group at C_{10} (Cf. Fig. 2), it would be affected by the conformation of B ring. Inspection of Dreiding models shows that two conformations of the B ring are

* NMR spectra were taken on a Varian A-60 spectrometer in $CDCl_3$. Chemical shifts are experessed in δ (ppm) downfield from TMS used as internal reference.

possible, one upward and the other downward boat (Cf. Fig. 3). With respect to the long range shielding effects of the CO function, one of the two downward boat structure, (a) and (b), is possible for I which shows the lower chemical shift of C_{11}-Me.

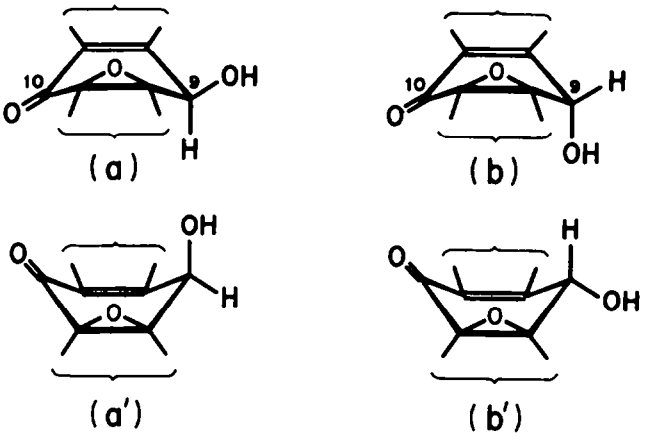


FIG. 3 The conformations of B ring.

Similarly, one of the two possible upward boat structures, (a') and (b'), is possible for VIII. Moreover, regarding to the configuration at C_9, (a) and (b) are identical with (a') and (b'), respectively. Accordingly, if I is (a), VIII must be (b'), and if I is (b), then VIII must be (a'). Namely, the configurations of I and VIII at C_9 must be decided by the determination whether the conformations of both C_9-OH groups are quasiaxial or quasiequatorial.

The transformation of the B ring is possibly originated in some steric factors such as the stabilization due to intramolecular H-bonding, which is suggested by the spin-coupling between C_9-OH and C_9-H. In order to ascertain the existence of the H-bonding the IR spectra of X and XI were measured under varying conditions as summarized in Table 1. The Table clearly shows that any free OH band is not present

TABLE 1

Compound	Solvent	Thickness of cell (mm)	ν(OH)[a] cm^{-1}		
X	$CHCl_3$	0·25	3550(w)	3406	3456
X	$CHCl_3$	5	3559(w)	3401	3451
X	$Cl_2C{=}CCl_2$	20	3562(w)	3409	3472
X	CCl_4	20	e	3409	3468
XI	$CHCl_3$	0·25	—	3325	3530
XI	$CHCl_3$	5	—	3326	3530
XI	$Cl_2C{=}CCl_2$	20	—	3333	3528
XI	CCl_4	insoluble			

[a] The bonded band of C_8—OH is omitted, because it appears in the region of 3200–2900 cm^{-1} as a broad band due to chelation.

in the spectra of both compounds and that the OH stretching bands are essentially unaffected by the changing concentration. Since the concentration for the IR spectrum in 0·25 mm cell is the same with that used for NMR measurement, the C_8-OH and C_9-OH of X and XI take part in intramolecular H-bonding even under the concentration used for NMR measurement. Inspection of Dreiding models suggests that the explanation of the absence of the free OH band in the spectra is difficult unless the conformation of the both C_9-OH is quasiequatorial. Consequently, the structures of the C_9-normal compounds (I and X) and C_9-epi compounds (VIII and XI) must be shown as Fig. 3(a) and Fig. 3(b'), respectively.

Although the configuration at C_9 has been elucidated as above, yet the assignment of the H-bonded bands remains uncertain, but should give the more positive proof of the stereochemistry. Concerning the H-bonding aspect of the C_8- and C_9-OH groups, the inconceivable behaviour of the phenolic OH groups in the NMR spectra are significant. The $C_{8'}$-OH signals of C_9-epi compounds (VIII and XI) appear at 12·53 ppm, and the chemical shifts agree with those of Q_1 unit (IX: 12·50 ppm). On the contrary, the corresponding signals of C_9-normal compounds (I and X) show a considerable downfield shift (Cf. Table 2), which disappears on acetylation of C_8-OH

TABLE 2

Compound	Configuration of C_9-OH	δ (ppm) C_8-OH	$C_{8'}$-OH
I	normal (β)	7·13	12·96
X	normal	7·09	13·08
III	normal	—	12·40
IV	normal	—	12·41
V	normal	8·70	12·50
VIII	epi (α)	8·73	12·53
XI	epi	8·73	12·53

(Cf. III and IV), and of C_9-OH (Cf. V). On the other hand, the C_8-OH proton signals of I and X appear at a higher field than those of the compounds (VIII, XI and V), which show the $C_{8'}$-OH signals at normal position.

These observations suggest that the C_8-OH groups of I and X would have an interaction with $C_{8'}$-OH, while those of C_9-epi compounds would interact with C_9-OH. In the case of V, the C_8-OH group possibly bonds to C_9-OAc due to favourable conformation of the acetoxyl group.

In order to confirm the assumption, several model compounds were synthesized. The compounds and the chemical shifts* of the phenolic OH groups are shown in Chart 3.

The C_2-OH proton signals of XV and XIX, in which the H-bonding of $C_{2'}$-OH to C_2-OH is expected, show the considerable downfield shift compared with those of

* Except XXI, the spectra were taken at a concentration of 30 mg/0·4 ml in $CDCl_3$. As for prominent compounds (XV, XVII, XIX and XX), the spectra were also taken on dilution to 1/10 and 1/50, but the signals (sharp singlet) showed no change.

XIV and XVIII, and the shift disappears on acetylation of $C_{2'}$-OH (Cf. XVI). This result is consistent with the behaviour of the $C_{8'}$-OH proton signals of I and X (Cf. Table 2). Further, the phenolic OH groups which have H-bonding with the O atom placed at the ortho benzylic C atom reveal different chemical shifts from those of the

CHART 3

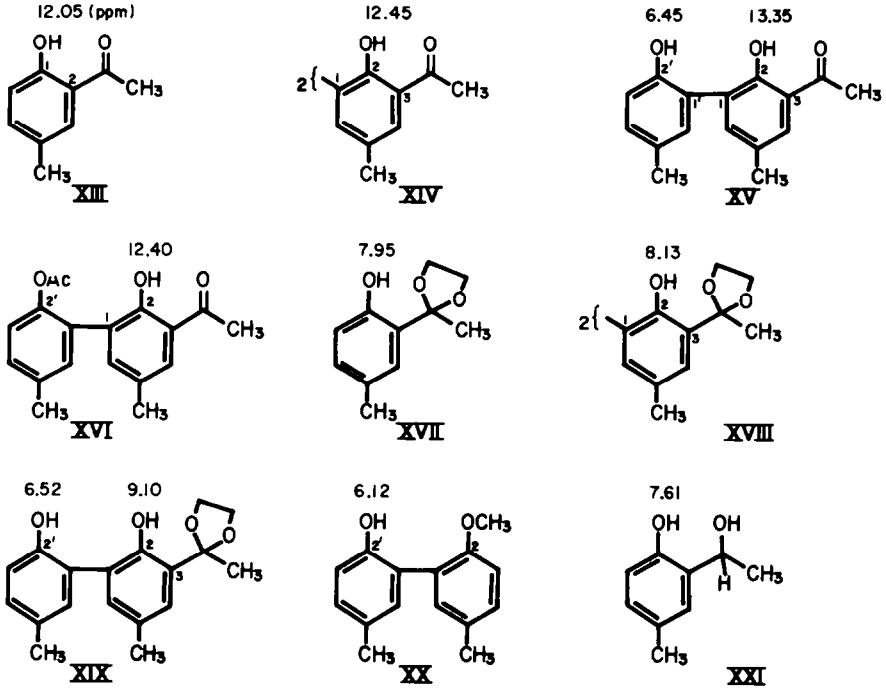
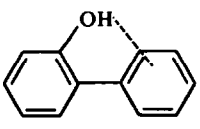
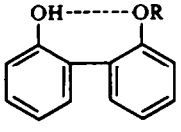
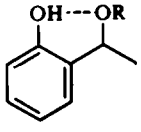


TABLE 3. THE INTRAMOLECULAR H-BONDING BANDS OF THE PHENOLIC COMPOUNDS (in cm^{-1})

Compound			
XV	3574[a] (3559)[b]	3420 (3391)	ca. 3000
XIX	3564 (3550)	3373 (e)[c]	3285 (e)[c]
XX	3558 (3549)	3435 (3396)	—
XVII	—	—	3406 (3386)
XVIII	—	—	3395 (3364)
XXI	—	—	3426 (3394)

[a] Measured in CCl_4 with 20 mm cell.
[b] Measured in $CHCl_3$ with 5 mm cell (written in parenthese).
[c] Broad band at 3291 cm^{-1} due to overlapping.

OH groups which bond to the OH or OR oxygen atom attached to another benzene ring (Cf. XV, XIX and XX). The signals of the former group, though they lie in a wide range according to the nature of the acceptor, generally appear in a lower field than the latter. These facts clearly explain the difference of the chemical shifts of C_8-OH between C_9-normal and C_9-epi compounds.

Table 3 shows the OH stretching frequencies of the model compounds in dilute solution. The phenolic OH groups bonded to oxygen functions generally appear within a range of 2900–3435 cm^{-1} (in CCl_4), and all the compounds, in which the interaction between $C_{2'}$-OH and C_2-OR is suggested by NMR, exhibit bonded bands of $C_{2'}$-OH to π electron of other benzene ring though they are very weak (Cf. XV, XIX and XX).

From this evidence, the more strongly bonded bands of X (at 3409 cm^{-1}) and XI (at 3333 cm^{-1}) are reasonably assigned as C_8-OH bonded to $C_{8'}$-OH and as C_8-OH bonded to C_9-OH, respectively, and the weak band of X at 3562 cm^{-1} is confirmed as

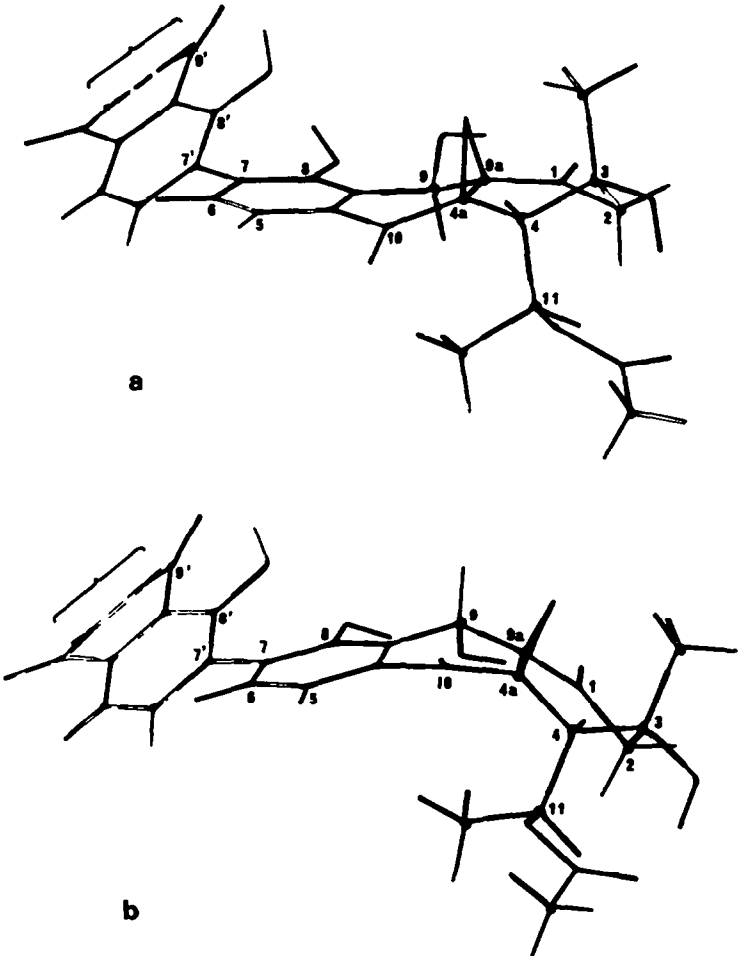
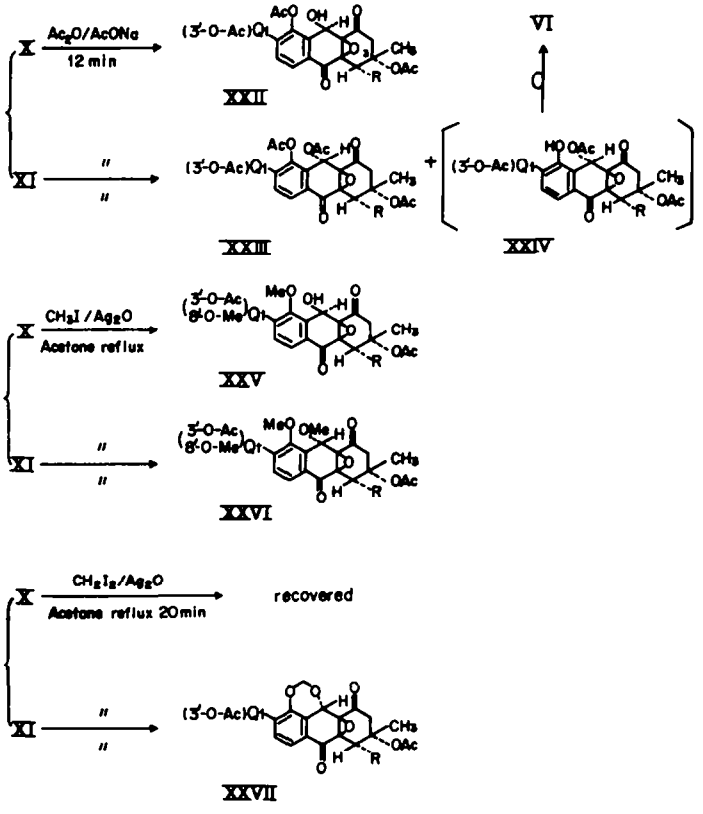


FIG. 4.

C_8-OH bonded to π electron of C′ ring. Thus, the remaining bonded bands of X (at 3472 cm^{-1}) and XI (at 3528 cm^{-1}) must be attributed to the respective C_9-OH groups bonded to CO at C_1. The distances between the two functions in respective compounds are approximately estimated as 2·0 Å and 1·7 Å from molecular models, therefore, providing that the $\Delta\nu$ value ($\nu_{\text{free OH}}-\nu_{\text{bonded OH}}$) only depends on the distance between OH and acceptor, the above assignment seems improper. Recently, however, Ōki *et al.* reported[5] that in H-bonding between OH and CO groups $\Delta\nu$ is a function of $\cos\theta/R$ (θ: angle between the plane of CO lone pair and OH, R: distance between OH and CO in Å). In the case of XI, a considerable θ value is predicted from Dreiding models in contrast with 0° in X (Cf. Fig. 4). Accordingly, there would be no objection to the above-mentioned assignment of the H-bonding bands.

Since the aromatic proton signals of the NMR spectra of I, VIII, X and XI show the same pattern, these four compounds should have a similar conformation about the biphenyl linking, and the interaction between C_8-OH and $C_{8'}$-OH in compounds I and X suggests that the biphenyl conformation is *cis* for the most part* (Cf. Fig. 4). Therefore, it is unlikely that the difference in the H-bonding aspects of C_8-OH

CHART 4



* One of the two possible *cis* conformations is shown in Fig. 4. In the case of C_9-normal compounds, it is partly in nearly perpendicular biphenyl conformations as mentioned above.

between C_9-normal and C_9-epi compounds is owing to the biphenyl conformation. Consequently, it could be attributed to some steric factor of the C_9-OH groups of both epimers. Although the conformations of the C_9-OH groups seem the same from Dreiding models, in virtual molecules of the C_9-normal compounds the β-OH group at C_9 is possibly hindered from approaching the C_8-OH due to the non-bonded interaction between the CO group at C_{10} and the C_{11}-Me group (Cf. Fig. 4a). On the other hand, the C_9-epi compounds are free from such interaction, and the C_8-OH prefers the bonding with C_9-OH to the bonding with $C_{8'}$-OH as observed in model compounds.

In connection with above discussions, the reactivities of the C_8- and C_9-OH groups of X and XI were examined as shown in Chart 4. Under the conditions in which X gave only the 8-O-acetyl compound (XXII), XI afforded the 8,9-O-diacetyl compound (XXIII) and the 9-O-acetyl derivative (XXIV), which was epimerized into VI on TLC, but the corresponding 8-O-acetate was not detected. The methylation of X gave 8,8'-O-dimethyl ether (XXV), whereas that of XI yielded 8,8',9-O-trimethyl ether (XXVI). Further, on treatment with methylene iodide XI only gave 8,9-methylenedioxy compound (XXVII).

This chemical evidence supports the stereochemistry concluded from spectroscopic examinations, and the favourable conformation of I and its C_9-epimer are reasonably shown as Figs 4a and 4b (or their alternative *cis* conformers about 7,7'-linking), respectively.

This study confirms the structures of julichromes $Q_{2\cdot3}$ and $Q_{3\cdot4}$[1] which have Q_3 unit in the molecules.

EXPERIMENTAL*

Acetylation products of I

(i) 8,8',9-O-*Triacetate* (II). A soln of 20 mg I in 2 ml Ac_2O and one ml pyridine was stirred at room temp for 1 hr. The reaction mixture was poured into H_2O, and the ppt was extracted with $CHCl_3$. The crude acetate (15 mg) from the $CHCl_3$ soln was recrystallized from MeOH to give 6 mg II as yellow prisms, m.p. >300° (on hot stage). (Found: C, 61·28; H, 5·04. $C_{44}H_{42}O_{18}$ requires: C, 61·53; H, 4·93%).

No chelated CO band was observed in its IR spectrum. On continuous development TLC for 18 hr using $CHCl_3$-acetone (85:15), II was completely converted to 8,9-O-diacetate (IV).

(ii) 8-O-*Acetate* (III). A soln of 26 mg I in about 5 ml $CHCl_3$ was evaporated, and the residue was dissolved in 2·5 ml Ac_2O. To the soln, 20 mg of freshly fused AcONa was added, and the mixture was stirred at room temp for 12 min. The mixture was poured into H_2O, and the ppt was extracted with EtOAc. The crude product (28 mg) from the extract was separated by continuous development TLC using $CHCl_3$–MeOH (95:5). The upper zone gave 3 mg 8,9-O-diacetate (IV) (mentioned below), and the bottom zone gave 22 mg III, which was recrystallized from MeOH to afford orange prisms, m.p. >280° (on hot stage). (Found: C, 61·92; H, 5·28. $C_{40}H_{38}O_{16}$ requires: C, 62·01; H, 4·94%).

The NMR spectrum showed the C_8-OAc signal at 2·10 ppm and the disappearance of the C_8-OH signal of I.

(iii) 8,9-O-*Diacetate* (IV). To a soln of 40 mg I in 4 ml Ac_2O, 40 mg of fused AcONa was added, and the mixture was stirred at room temp for 1·5 hr. Working up as usual gave 48 mg red product, which was separated by continuous development TLC using CHCl–MeOH (95:5). The product (28 mg) from the main zone was recrystallized from benzene to give 21 mg IV as orange prisms, m.p. 170–173° (on hot stage). (Found: C, 61·81; H, 4·96. $C_{42}H_{40}O_{17}$ requires: C, 61·76; H, 4·94%).

The NMR spectrum showed C_8-OAc at 2·07 ppm, and C_9-OAc at 1·97 ppm and the absence of the signals due to C_8-OH and C_9-OH. IV gave II on treatment with Ac_2O-pyridine for 15 min.

* All m.ps and b.ps are uncorrected. Unless otherwise stated, Yamanilayer-PG (Yamani Chem. Co. Osaka, Japan) was used for preparative TLC on metal free silica gel.

(iv) 9-O-*Acetate* (V). To a soln of 118 mg I in 2 ml Ac_2O 5 mg *p*-TsOH was added, and the mixture was stirred at room temp for 5 min. The mixture was poured into 250 ml H_2O, and the red ppt was collected washed with H_2O and dried. The continuous development TLC in $CHCl_3$–MeOH (96:4) showed two main red zones, and from the bottom zone 36 mg I was recovered. The upper zone gave 42 mg V, which was further purified for analysis with $CHCl_3$–n-hexane to afford a red amorphous powder. (Found: C, 61·74; H, 5·22. $C_{40}H_{38}O_{16}$ requires: C, 62·01; H, 4·94%). On acetylation with Ac_2O–AcONa for 1·5 hr, this compound gave IV.

(v) 3,3',9-O-*Triacetate* (VI). A mixture of 100 mg I, 5 ml Ac_2O and 30 mg *p*-TsOH was stirred at room temp for 1·5 hr. Working up as above gave about 110 mg crude acetate, which was separated by continuous development TLC using $CHCl_3$–MeOH (98:2). From the main zone 73 mg almost pure VI was obtained. For analysis, it was purified from ether–n-hexane to give orange powder, m.p. 191–192° (on hot stage). (Found: C, 61·30; H, 5·00. $C_{44}H_{42}O_{18}$ requires: C, 61·53; H, 4·93%).

(vi) 3,3',8,8',9-O-*Pentaacetate* (VII). A soln of 43 mg VI in 2ml Ac_2O and one ml pyridine was stirred at room temp for 1 hr. After decomposition of excess Ac_2O with H_2O, the mixture was extracted with EtOAc to give 50 mg crude acetate. Recrystallization from MeOH afforded 26 mg VII as yellow prisms, m.p. >300° (on hot stage). (Found: C, 61·14; H, 4·75. $C_{48}H_{46}O_{20}$ requires: C, 61·14; H, 4·92%). IR and NMR spectra showed the absence of OH group.

This pentaacetate was also obtained from II on treatment with Ac_2O and *p*-TsOH for 1 hr.

Hydrolysis of V.

A soln of 78 mg V in 80 ml of 90% acetone–H_2O was refluxed for 6 hr. After removal of the acetone, the residue was extracted with EtOAc to give 80 mg crude product, which was separated by continuous development TLC using $CHCl_3$–MeOH (96:4). The TLC showed two main zones; the bottom zone gave 18 mg I, which was identical with authentic sample, and the upper zone afforded 24 mg VIII. For analysis VIII was recrystallized from MeOH to give reddish orange needles, m.p. >300° (on hot stage). (Found: C, 62·24; H, 4·93. $C_{38}H_{36}O_{15}$ requires: C, 62·29; H, 4·95%). UV λ_{max}^{MeOH} mμ (log ε) 217 (4·54) max, 250 (4·39) inflection, 270 (4·32) inflection, 320 (3·85) inflection, 450 (3·79) max.

Oxidation of VIII *to* IX.

To a hot soln of 5 mg VIII in 0·15 ml AcOH 0·1 ml of 7% $K_2Cr_2O_7$ in AcOH was added. The mixture was heated on a boiling water bath for 15 min and then poured into H_2O. Extraction with EtOAc gave 3·5 crude product, which was separated by continuous development TLC using $CHCl_3$–MeOH (96:4). In this procedure 1·5 mg IX identical with authentic specimen was isolated.

Hydrolysis of VI *to* X *and* XI.

A soln of 200 mg VI in 45 ml 90% acetone–H_2O was refluxed for 6 hr. Working up as described above gave about 200 mg crude product, which was separated into two main zones by continuous development TLC using $CHCl_3$–MeOH (98:2). The first red zone afforded 57 mg XI, which was recrystallized from CCl_4 to give orange prisms, m.p. 158–162° (on hot stage). (Found: C, 53·29; H, 4·17; Cl, 14·71. $C_{42}H_{40}O_{17}\cdot CCl_4$ require: C, 53·21; H, 4·17; Cl, 14·61%).

From the second red zone. 54 mg X was obtained. For analysis, it was purified from CCl_4–n-hexane to yield orange powder, m.p. 160–165° (on hot stage). (Found: C, 61·95; H, 5·04. $C_{42}H_{40}O_{17}$ requires: C, 61·76; H, 4·94%).

Oxidation of X *to* XII.

A soln of 12 mg X in one ml AcOH was treated with a soln of 2 mg $K_2Cr_2O_7$ in 0·5 ml AcOH at 100°. After 18 min, the reaction mixture was poured into H_2O and extracted with $CHCl_3$. Evaporation of the $CHCl_3$ and purification by continuous development TLC using $CHCl_3$–MeOH (98·5:1·5) afforded 4 mg XII, which was identical with authentic sample.

Oxidation of XI *to* XII.

In the similar method described above, 12 mg XI gave 4 mg XII.

Preparation of model compounds (XIII–XXI)

Compound XIII. This was prepared from *p*-cresol according to the literature.[6] (Found: C, 71·85; H, 6·77. Calc. for $C_9H_{10}O_2$: C, 71·98; H, 6·71%).

Compounds XIV *and* XV. To a soln of 3·24 g *p*-cresol in 600 ml 5% KOH a soln of 8·25 g I_2 and 19·5 g KI in 600 ml H_2O was added with stirring at 0°. After additional 30 min the mixture was acidified with 10% HCl and extracted with ether. The product (about 8 g) was purified by preparative GC on 5% PEG-6000 to afford 4·8 g 2-iodo-4-methylphenol as an oil. The treatment with *p*-TsCl-pyridine and recrystallization of the product from MeOH gave the corresponding tosylate in almost quantitative yield as colourless prisms, m.p. 108–109°. (Found: C, 43·59; H, 3·40; I, 33·02; S, 8·41. $C_{14}H_{13}O_3IS$ requires: C, 43·31; H, 3·38; I, 32·68; S, 8·26%).

This tosylate (4·0 g) was heated at 200–250° with 4·0 g Cu powder for 30 min. The product was chromatographed on 28 g silica gel with benzene. Evaporation of the benzene and recrystallization from MeOH gave 2·35 g 5,5'-dimethyl-2,2'-ditosyloxybiphenyl as colourless needles, m.p. 165–165·5°. (Found: C, 64·34; H, 5·00; S, 12·26. $C_{28}H_{26}O_6S_2$ requires: C, 64·35; H, 5·01; S, 12·27%).

This biphenyl compound (1·9 g) was refluxed with a soln of 3 g KOH in 50 ml MeOH for 4 hr. Distillation of the hydrolysed product (770 mg) gave pure 2,2'-dihydroxy-5,5'-dimethylbiphenyl as colourless prisms, b.p. 180° (bath temp), m.p. 156–157°. (Found: C, 78·32; H, 6·52. $C_{14}H_{14}O_2$ requires: C, 78·48; H, 6·59%).

This compound (100 mg) was converted to the diacetate with Ac_2O-pyridine, and the acetate was heated with a soln of 150 mg $AlCl_3$ in 0·6 ml nitrobenzene at 120° for 2 hr. The mixture was poured into dil HCl and extracted with $CHCl_3$. The oily product from the extract was hydrolysed with methanolic KOH, and then nitrobenzene was removed by steam distillation. The residue was acidified with 10% HCl and extracted with ether to afford 124 mg yellow oily product, which was separated by TLC on kieselgel G-F using $CHCl_3$–MeOH (96:4).

The first zone gave 13 mg XIV, which was recrystallized from MeOH to afford yellow needles, m.p. 189·5–190°. (Found; C, 72·40; H, 6·03. $C_{18}H_{18}O_4$ requires: C, 72·46; H, 6·08%).

The second zone afforded 72 mg XV, which was recrystallized from n-hexane to give 63 mg pure sample as pale yellow prisms, m.p. 129–130°. (Found: C, 75·16; H, 6·37. $C_{16}H_{16}O_3$ requires: C, 74·98; H, 6·29%).

The compound XIV was also obtained by hydrolysis of XVIII (mentioned below).

Compound XVI. A soln of 50 mg XV in one ml pyridine was stirred with 50 mg freshly fused AcONa for 1 hr. Working up as usual gave 55 mg XVI as pale yellow oil, $b.p._{10-5}$ 120° (bath temp). (Found: C, 72·63; H, 6·08. $C_{18}H_{18}O_4$ requires: C, 72·46; H, 6·08%).

Compound XVII. To a soln of 500 mg XIII in 12 ml benzene 120 mg NaH was added with stirring, and the mixture was refluxed with 960 mg *p*-TsCl for 15 min. The excess *p*-TsCl was decomposed with pyridine-H_2O, and the mixture was acidified with 10% HCl. Extraction with benzene, evaporation of the solvent and recrystallization from MeOH gave 983 mg of tosylate as colourless prisms, m.p. 117·5–118°. (Found: C, 63·29; H, 5·32; S, 10·50. $C_{16}H_{16}O_4S$ requires: C, 63·14; H, 5·30; S, 10·53%).

The tosylate (303 mg) was heated, in benzene, with 0·5 ml ethylene glycol and 190 mg *p*-TsOH for 3 hr, removing water azeotropically. The mixture was poured into dil NH_4OH, and the benzene layer afforded 348 mg crude product, which was recrystallized from MeOH to give 300 mg pure ketal as colourless prisms, m.p. 90–91°. (Found: C, 61·91; H, 5·77. $C_{18}H_{20}O_5S$ requires: C, 62·02; H, 5·92%).

The ketal (68 mg) was refluxed in 3 ml MeOH with 100 mg KOH for 2·5 hr. After removal of MeOH, the residue was dissolved in H_2O, saturated with CO_2 and extracted with ether. On distillation the extract gave XVII as colourless prisms, $b.p._1$ 90–100° (bath temp), m.p. 48–51°. (Found: C, 68·02; H, 7·25. $C_{11}H_{14}O_3$ requires: C, 68·02; H, 7·27%).

Compound XVIII. To a soln of 950 mg XVII in 100 ml of 5% KOH a soln of 1·37 g I_2 and 3·25 KI in 100 ml H_2O was added with stirring at 5°. After 1·5 hr the mixture was filtered and the filtrate was staurated with CO_2 to give white ppt, which was recrystallized from MeOH to afford 1·26 g ethylene ketal of 2-hydroxy-3-iodo-5-methylacetophenone as colourless prisms, m.p. 101–102°. (Found: C, 41·57; H, 4·19; I, 39·28. $C_{11}H_{13}O_3I$ requires: C, 41·27; H, 4·09; I, 39·65%).

This iodo compound (896 mg) was acetylated with Ac_2O-pyridine at room temp for 18 hr. Working up as usual and recrystallization from n-hexane gave 750 mg pure acetate as colourless prisms, m.p. 90·5–91·5°. (Found: C, 43·22; H, 4·21; I, 34·87. $C_{13}H_{15}O_4I$ requires: C, 43·11; H, 4·17; I, 35·04%).

A mixture of 957 mg this acetate and 800 mg Cu powder was packed in a glass tube (D: 6 mm), and the top of the mixture was covered with additional 150 mg Cu powder. The tube was heated at 200–250° for 30 min. The crude product (800 mg) was fractionated on 20 g silica gel column. After elution of 113 mg unchanged material (with benzene) and 50 mg of unidentified material (with $CHCl_3$), 403 mg crude biphenyl compound was eluted with $CHCl_3$–EtOAc (75:25). Recrystallization from n-hexane gave 350 mg of pure product as colourless prisms, m.p. 122·5–123·5°. (Found: C, 66·29; H, 6·45. $C_{26}H_{30}O_8$ requires: C, 66·37; H, 6·43%).

This biphenyl compound (100 mg) was hydrolysed with a soln of 150 mg KOH in 5 ml MeOH by stirring at room temp for 1 hr. The solvent was removed, and the residue was dissolved in H_2O and treated with CO_2. The ppt was recrystallized from MeOH to give 64 mg XVIII as colourless needles, m.p. 169·5–170°. (Found: C, 68·61; H, 6·87. $C_{22}H_{26}O_6$ requires: C, 68·38; H, 6·78%).

This compound was hydrolysed to XIV with MeOH–HCl in almost quantitative yield.

Compound XIX. To a soln of 63 mg XV in 4 ml benzene 20 mg NaH and successive 165 mg *p*-TsCl were added with stirring, and the mixture was refluxed for 3 hr. After decomposition of the excess *p*-TsCl with pyridine-H_2O, the mixture was acidified with 10% HCl and extracted with ether to afford 140 mg of almost pure ditosylate. For analysis, small sample was recrystallized from ether to give colourless prisms, m.p. 81–82°. (Found: C, 63·77; H, 5·49; S, 10·63. $C_{30}H_{28}O_7S_2 \cdot \frac{1}{4}C_2H_5OC_2H_5$ requires: C, 63·87; H, 5·53; S, 10·66%).

A soln of 140 mg above-mentioned ditosylate in 11 ml benzene was refluxed with 0·5 ml ethylene glycol and 48 mg *p*-TsOH for 3 hr removing water azeotropically. Working up as usual gave 193 mg crude oily product, which was recrystallized from ether to afford 126 mg of the corresponding ketal as colourless plates, m.p. 156–157°. (Found: C, 63·21; H, 5·37; S, 10·58. $C_{32}H_{32}O_8S_2$ requires: C, 63·13; H, 5·30; S, 10·54%).

This ketal derivative (120 mg) was refluxed with a soln of 400 mg KOH in 5 ml MeOH for 3 hr. After evaporation of the solvent the residue was dissolved in H_2O and treated with CO_2. The ppt was extracted with ether to give 55 mg yellow oily XIX, which was purified by distillation to give colourless oil, $b.p._{10^{-4}}$ 150° (bath temp). (Found: C, 71·74; H, 6·68. $C_{18}H_{20}O_4$ requires: C, 71·98; H, 6·71%).

Compound XX. To a soln of 100 mg 2,2'-dihydroxy-5,5'-dimethylbiphenyl (above-mentioned) in 3 ml benzene 13 mg NaH and 120 mg Me_2SO_4 were added, and the mixture was stirred at room temp for 1·5 hr. After decomposition of the excess Me_2SO_4 with 28% NH_4OH, the mixture was acidified with 10% HCl and extracted with benzene. The colourless oil (99 mg) from the extract was separated by TLC on Kieselgel G-F using $CHCl_3$. The second zone gave 71 mg oily product, which was distilled to afford pure XX as colourless prisms, $b.p._1$ 145° (bath temp), m.p. 79–80°. (Found: C, 78·94; H, 7·08. $C_{15}H_{16}O_2$ requires: C, 78·92; H, 7·06%).

Compound XXI. A soln of 140 mg 5-methyl-2-tosyloxyacetophenone (above-mentioned) in 10 ml MeOH was treated with 30 mg $NaBH_4$ at room temp for 2 hr. The solvent was distilled off *in vacuo*, and the residue was acidified with 10% HCl. Extraction with benzene gave 146 mg colourless oily product, which was crystallized from n-hexane to afford colourless prisms, m.p. 96·5–97°. (Found: C, 62·51; H, 5·91. $C_{16}H_{18}O_4S$ requires: C, 62·72; H, 5·92%).

This compound (200 mg) was refluxed with a soln of 200 mg KOH in 3 ml MeOH for 2 hr. Working up as usual followed by recrystallization from ether–n-hexane gave 72 mg XXI as colourless prisms, m.p. 104–105°. (Found: C, 71·19; H, 8·06. $C_9H_{12}O_2$ requires: C, 71·02; H, 7·95%).

Acetylation of X *with* Ac_2O–AcONa.

A mixture of 46 mg X and 50 mg of freshly fused AcONa in 5 ml Ac_2O was stirred at room temp for 12 min. The mixture was poured into H_2O and extracted with EtOAc to give 54 mg crude acetate, which was separated by continuous development TLC using $CHCl_3$–MeOH (98:2). The main zone gave 39 mg almost pure XXII. For analysis it was recrystallized from MeOH to afford orange prisms, m.p. 244–245° (on hot stage). (Found: C, 61·74; H, 5·21. $C_{44}H_{42}O_{18}$ requires: C, 61·53; H, 4·93%).

NMR δ (ppm): 12·40 (C_8-OH); 3·58 (C_9-OH); 2·10 (C_8-OAc).

Acetylation of XI *with* Ac_2O–AcONa.

The compound XI (50 mg) was treated with 5 ml Ac_2O and 50 mg AcONa as above. The crude product (64 mg) was separated by continuous development TLC using $CHCl_3$–MeOH (98:2). The compound (12 mg) from the first zone was identified as VI by IR spectrum, and the second zone gave 20 mg XXIII, which was recrystallized from ether–n-hexane to afford pure XXIII as orange prisms, m.p. 153–158° (on hot stage). (Found: C, 61·51; H, 5·09. $C_{46}H_{44}O_{19}$ requires: C, 61·33; H, 4·92%), NMR δ (ppm): 12·38 (C_8-OH); 2·11 (C_8-OAc); 1·97 (C_9-OAc).

The IR spectrum showed no absorption band in ordinary OH stretching region.

The compound (17 mg) from the bottom zone of TLC seemed XXIV, but it was difficult to purify because it gradually changed to VI on further TLC.

Methylation of X.

To a soln of 40 mg X in 7 ml acetone 7 mg MeI and Ag_2O from 300 mg $AgNO_3$ were added, and the

mixture was refluxed with stirring for 30 min. The mixture was filtered, and the crude product from the filtrate was separated by continuous development TLC using $CHCl_3$–MeOH (98:2). The main yellow zone gave 23 mg almost pure XXV. For analysis, it was purified from $CHCl_3$–n-hexane to give yellow prisms, m.p. 143–145° (on hot stage). (Found: C, 62·34; H, 5·40; MeO, 7·14. $C_{44}H_{44}O_{17}$ requires: C, 62·55; H, 5·25; MeO, 7·53%). NMR δ (ppm): 3·57 (C_8-OMe); 3·72 (C_8-OMe).

Methylation of XI.

Compound XI (40 mg) was methylated as above. Purification of the product by continuous development TLC using $CHCl_3$–MeOH (98·5:1·5) gave 32 mg XXVI. For analysis, it was recrystallized from MeOH to yield needles, m.p. 180–180·5° (on hot stage). (Found: C, 63·07; H, 5·43; MeO, 10·48. $C_{45}H_{46}O_{17}$ requires: C, 62·93; H, 5·40; MeO, 10·84%). NMR δ (ppm): 3·53 (C_8-OMe); 3·63 (C_9-OMe); 3·73 (C_8-OMe). No OH band was observed in IR spectrum.

Treatment of XI *with methylene iodide* (XXVII).

A mixture of 58 mg XI, 2 ml CH_2I_2 and Ag_2O (prepared from 400 mg $AgNO_3$) in 7 ml acetone was refluxed with stirring for 20 min. The mixture was filtered, and the filtrate was evaporated in the presence of H_2O *in vacuo* to remove excess CH_2I_2. The residue (59 mg) was separated by continuous development TLC using $CHCl_3$–MeOH (97·5:2·5). The TLC showed several zones, most of which were unidentified. The material (15 mg) from the main red zone was reseparated by the same method to afford 10 mg XXVII, which was purified from $CHCl_3$–n-hexane to give orange powder, m.p. 165–173° (on hot stage). (Found: C, 62·13; H, 5·07. $C_{43}H_{40}O_{17}$ requires: C, 62·31; H, 4·87%). No OH band was observed in the IR spectrum, but the presence of the peri-OH quinonoid structure was confirmed by chelated CO band at 1638 cm^{-1} and by positive colour reaction with $Mg(OAc)_2$.

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