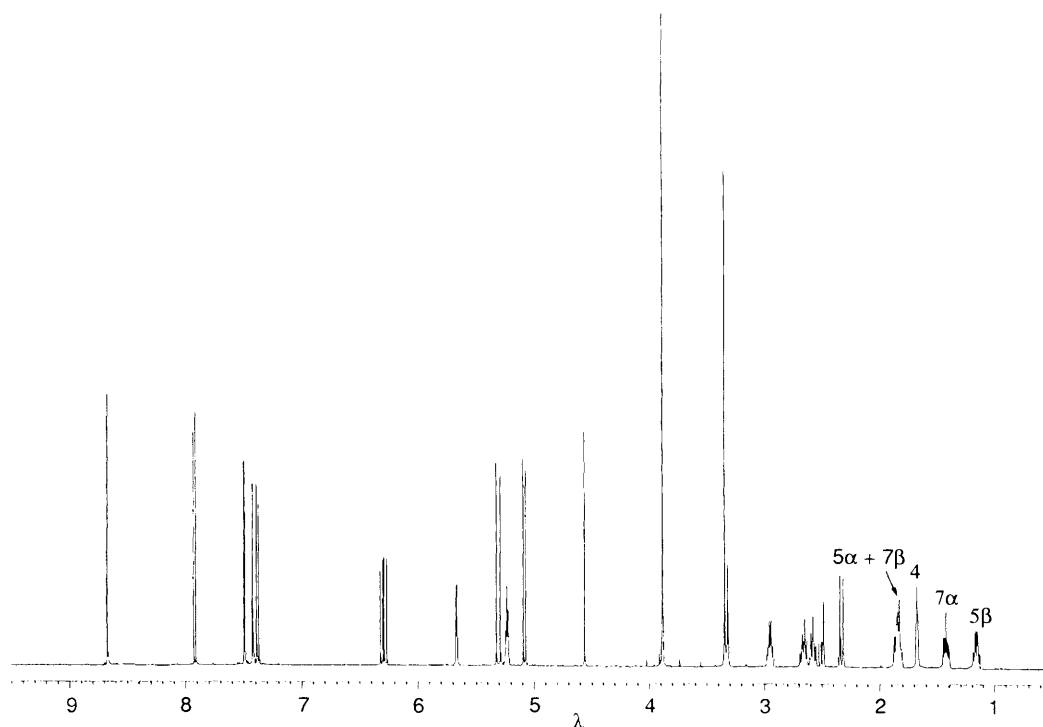




**Table 1**  $^1\text{H}$  and  $^{13}\text{C}$  NMR assignments for quinidine **1a** and (3*S*)-3-hydroxyquinidine **5a** in  $[\text{}^2\text{H}_6]\text{DMSO}^a$ 

Carbon	$^1\text{H}$ NMR				$^{13}\text{C}$ NMR	
	<b>1a</b>		<b>5a</b>		<b>5a</b>	<b>1a</b>
	$\delta$	mult., <i>J</i> /Hz	$\delta$	mult., <i>J</i> /Hz		
2 <i>syn</i>	3.00	m	3.34	d, 12.3		
2 <i>anti</i>	2.70	br dd	2.33	d, 14.2	48.3	56.9
3	2.18	br dd, 8.1, 16.4			39.1	70.9
4	1.68	br s	1.68	br s	27.8	33.3
5 $\alpha$	1.40	m	1.85	m	26.2	20.6
5 $\beta$	1.40	m	1.16	m		
6 $\alpha$ ,6 $\beta$	2.55, 2.63	m	2.58, 2.65	m	49.0	49.0
7 $\alpha$	1.40	m	1.44	m	23.3	24.7
7 $\beta$	1.90	dd, 13.1, 4.4	1.85	m		
8	2.98	m	2.95	dd, 8.2, 16.2	60.5	59.4
9	5.29	br m	5.23	d, 5.8	70.6	70.9
10	6.08	ddd, 17.3, 10.4, 7.9	6.30	dd, 10.7, 17.3	141.2	144.3
11 <i>cis</i>	5.06	br d, 10.3	5.08	dd, 10.7, 2.0		
11 <i>trans</i>	5.08	br d, 17.3	5.31	dd, 17.3, 2.0	114.3	112.0
2'	8.67	d, 4.5	8.67	d, 4.5	147.5	147.5
3'	7.49	d, 4.5	7.49	d, 4.5	118.9	118.9
4'					149.3	149.3
5'	7.45	d, 2.7	7.42	d, 2.7	102.4	102.4
6'					156.7	156.8
7'	7.37	dd, 2.7, 9.1	7.38	dd, 9.1, 2.7	120.9	120.9
8'	7.91	d, 9.1	7.92	d, 9.1	131.1	131.1
9'					127.0	126.9
10'					143.8	143.8
6'-OMe	3.89	s	3.89	s	55.3	55.3
9-OH	5.64	br s	5.67	br d, 4.7		

<sup>a</sup> Chemical shifts are reported as  $\delta$ -values in parts per million (ppm) relative to  $\text{SiMe}_4$  at 500 MHz for proton and at 125 MHz for carbon.

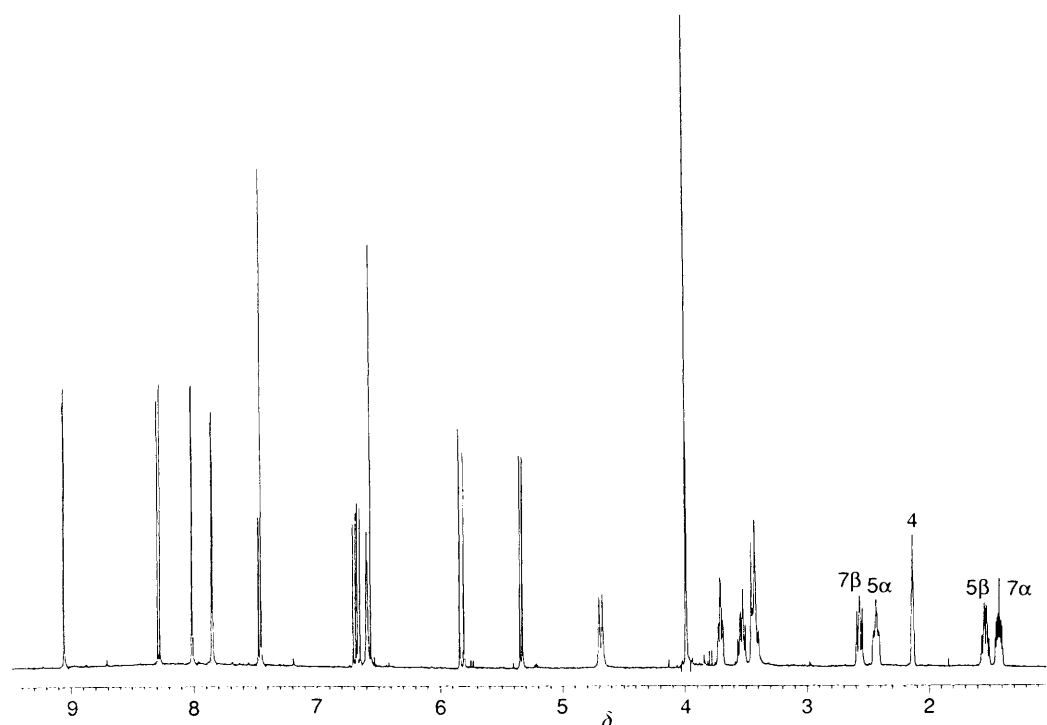
**Fig. 1** 500 MHz proton NMR spectrum of **5a** maleate in  $[\text{}^2\text{H}_6]\text{DMSO}$ 

methods for the cleavage of the  $\Delta^{3(10)}$ -olefinic bond. We found that the acetate **3b** was smoothly oxidized with osmium tetroxide-sodium periodate<sup>12</sup> in 80% acetic acid at 4 °C to give (8*R*,9*S*)-6'-methoxy-3-oxoruban-9-yl acetate **4** in 75% yield. Compound **4** showed the absence of olefinic protons in the  $^1\text{H}$  NMR spectrum and a strong peak at  $1735\text{ cm}^{-1}$  for the ketone carbonyl. Treatment of compound **4** with vinylmagnesium

bromide in dry tetrahydrofuran (THF) at 25 °C gave a 60:40 mixture of products **5a** and **6** in 80% yield, which was separated by chromatography on Florisil. The mass spectrum of product **6**, the first component eluted, was essentially identical with the spectrum of the quinidine metabolite; however, the TLC  $R_f$ -values, as well as the IR,  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectral properties of product **6**, although similar, were different from

**Table 2**  $^1\text{H}$  and  $^{13}\text{C}$  NMR assignments for quinidine **1a** maleate and (3*S*)-3-hydroxyquinidine **5a** maleate in degassed  $[\text{}^2\text{H}_5]\text{pyridine}^a$ 

Carbon	$^1\text{H}$ NMR				$^{13}\text{C}$ NMR	
	<b>1a</b> -maleate		<b>5a</b> -maleate		<b>1a</b> -maleate	<b>5a</b> -maleate
	$\delta$	mult., J/Hz	$\delta$	mult., J/Hz		
2 <i>syn</i>	4.52	br dd, 10.3, 9.3	4.68	br d, 13.7	49.3	57.4
2 <i>anti</i>	3.60	m	3.44	br d, 13.9		
3	2.62	m			37.8	70.8
4	1.90	br s	2.13	br s	28.0	34.4
5 $\alpha$	1.77	m	2.43	m		
5 $\beta$	1.77	m	1.53	m, 1.9, 10.4, 11.3	23.7	19.9
6 $\alpha$	3.33	dd, 9.3, 22.3	3.43	m	48.5	49.4
6 $\beta$	3.60	m	3.53	m, 9.4, 21.0		
7 $\alpha$	2.62	m	1.42	m	18.4	21.7
7 $\beta$	1.16	m	2.57	br t, 11.4		
8	3.78	t, 9.4	3.71	br t, 8.9	60.4	59.5
9	6.73	br s	6.59	br s	67.5	69.2
10	6.21	ddd, 10.3, 7.6, 17.5	6.68	dd, 10.7, 17.2	138.1	143.4
11 <i>cis</i>	5.24	d, 10.3	5.34	dd, 10.7, 1.5	116.9	113.9
11 <i>trans</i>	5.28	d, 17.3	5.82	17.3, 1.5		
2'	9.08	d, 4.4	9.05	d, 4.5	148.1	148.2
3'	8.02	d, 4.4	8.00	d, 4.5	119.4	119.4
4'					146.0	147.1
5'	7.66	d, 2.5	7.85	d, 2.6	101.2	102.1
6'					158.9	158.8
7'	7.47	dd, 2.5, 9.2	7.46	dd, 2.6, 9.2	122.6	122.3
8'	8.29	d, 9.2	8.28	d, 9.2	132.5	132.4
9'					126.5	126.9
10'					145.1	145.3
6'-OMe	3.96	s	3.99	s	56.2	56.2
maleate	6.58	s	6.56	s	169.7	169.5

<sup>a</sup> See footnote to Table 1.**Fig. 2** 500 MHz proton NMR spectrum of **5a** maleate in  $[\text{}^2\text{H}_5]\text{pyridine}$ 

those of the metabolite. It was clear from the method of synthesis, as well as the elemental analysis and spectral data, that compound **6** was the 3-hydroxy epimer of the metabolite. The second compound eluted from the column possessed m.p. TLC  $R_f$ -values, gas chromatographic retention time, IR,  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, and mass spectral properties identical with those of metabolite **5a**.<sup>13</sup>

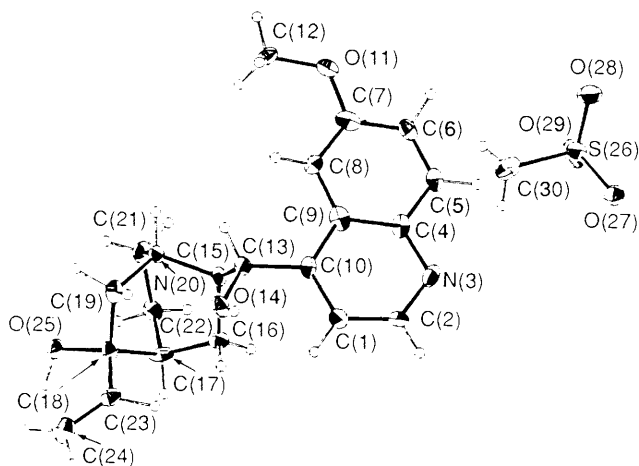
(3*S*)-Hydroxyquinidine was also obtained by microbial oxidation of quinidine using *Cunninghamella verticillata*. The crude yields were in the order of 1%. This material was found to be identical in all respects with the material prepared by chemical synthesis.

*NMR Study*.—In order to obtain unambiguous  $^1\text{H}$  NMR

**Table 3** NOE Study (NOEDIFF) of (3*S*)-3-hydroxyquinidine **5a** maleate in [2H<sub>5</sub>]pyridine<sup>a</sup>

Proton decoupled	$\delta$	Proton observed	$\delta$	Change (%)
5 $\alpha$	2.4	5 $\beta$	1.5	21.8
		7 $\alpha$	1.4	4.9
		4	2.1	3.4
		5 $\alpha$	2.4	25.9
5 $\beta$	1.5	7 $\beta$	2.6	27.4
		5 $\alpha$	2.4	6.7
		8	3.7	6.1
		4	2.1	5.4
7 $\alpha$	1.4	9	8.0	4.3
		7 $\alpha$	1.4	20.2
		10	6.7	11.0
		3'	8.0	5.1
8	3.7	9	8.0	3.5
		7 $\alpha$	1.4	5.8
		11 <i>cis</i>	5.3	6.5
		7 $\beta$	2.6	6.1
10	6.7	5'	7.8	5.8
		2'	9.1	21.6
		9	6.6	16.1
		2 <i>syn</i>	4.7	2.4
3'	8.0	11 <i>trans</i>	5.8	3.6
		8	3.8	6.0
		2 <i>syn</i>	4.7	2.5
		11 <i>trans</i>	5.8	3.1
5'	7.8			

<sup>a</sup> 5 mg/0.6 cm<sup>3</sup> of 100% deuterated [2H<sub>5</sub>]pyridine degassed and sealed.

**Fig. 3** ORTEP drawing of (3*S*)-3-hydroxyquinidine methanesulphonate (1:1) (**5a**·MeSO<sub>3</sub>H).

assignments of compound **5a**, the <sup>1</sup>H NMR assignments of quinidine **1a** obtained under identical conditions were required. The assignments for the <sup>1</sup>H NMR resonances for compounds **1a** and **5a** were achieved by using 2D homonuclear proton correlation (COSY)<sup>14,15</sup> and 2D proton/carbon correlation (HETCOR)<sup>16</sup> techniques; the results in [2H<sub>6</sub>]DMSO are shown in Table 1 and the <sup>1</sup>H 500 MHz spectrum in Fig. 1. A comparison of the <sup>1</sup>H spectra of compounds **1a** and **5a** showed significant shift differences for the 10-, 11-*trans*, 2-, and 5-proton multiplets as well as the loss of the 3-proton for compound **1a**. A downfield shift of 0.3 ppm for the 10-, 11-*trans* and 2-*syn* protons was observed for compound **5a** compared with the signal for quinidine, along with a -0.3 ppm shift for the 2-*anti*-proton. One of the 5-protons was also shifted by 0.5 ppm downfield. All <sup>13</sup>C assignments for compounds **1a** and **5a** were consistent with published <sup>13</sup>C data,<sup>17</sup> with the exception of the C-3' and C-7' carbons which were reassigned. Since the 7-protons are on the same side as the 3-vinyl group in structure **5a** and on the opposite side in compound **6**, we had hoped to

**Table 4** Values of important dihedral angles from the X-ray structure of (3*S*)-3-hydroxyquinidine methanesulphonate

Dihedral	Atoms	Value
Φ1	C(3')-C(4')-C(9)-C(8)	-94.9
Φ2	C(3')-C(4')-C(9)-O	27.4
Φ3	C(4')-C(9)-C(8)-N(1)	-157.7
Φ4	C(4')-C(9)-C(8)-C(7)	79.1
Φ5	O-C(9)-C(8)-N(1)	78.2
Φ6	H-C(9)-C(8)-H	88.6
Φ7	C(7')-C(6')-O-C	-177.6
Φ8	C(2)-C(3)-C(10)-C(11)	111.6
Φ9	N(1)-C(2)-C(3)-C(4)	12.7
Φ10	N(1)-C(6)-C(5)-C(4)	13.4
Φ11	N(1)-C(7)-C(8)-C(4)	11.7

establish the stereochemistry at C-3 by evaluating the NOE between the 7 $\beta$ - and 5 $\beta$ -proton with the 10-protons. Unfortunately, in [2H<sub>6</sub>]DMSO the overlap of the 5 $\alpha$ - and 7 $\beta$ -proton signals prevented such a study. In order to alleviate this problem the spectra of compound **5a** and its maleate were obtained in several solvent systems. Fortunately, we found a suitable separation for 7 $\beta$ - and 5 $\alpha$ -proton resonances in [2H<sub>5</sub>]pyridine (Fig. 2). Table 2 lists the <sup>1</sup>H and <sup>13</sup>C NMR assignments for **1a** maleate and **5a** maleate, again achieved by using the COSY<sup>14,15</sup> and HETCOR<sup>16</sup> techniques. The assignments for **1a** maleate are similar to those reported by Chazin and Colebrook for quinidine hydrochloride in [2H<sub>6</sub>]DMSO<sup>18</sup> and those for quinidine in [2H<sub>6</sub>]benzene reported by Dijkstra *et al.*<sup>19</sup> The results of the NOE study on **5a** maleate in [2H<sub>6</sub>]pyridine are shown in Table 3.

**X-Ray.**—Of various salts tried, only the methanesulphonate proved suitable for single-crystal X-ray structure determination. Fig. 3 shows an ORTEP drawing of the structure obtained. Table 4 lists some of the important dihedral angles which define the overall conformation of the compound.

**Molecular Modelling Studies.**—Models of quinidine **1a** and 3-hydroxyquinidine **5a** were constructed using the atomic coordinates obtained for these compounds from X-ray crystallographic studies.<sup>20</sup> The model structures were refined by an initial energy minimization using the MAXIMIN2 force-field.\*

Systematic conformational searches were then performed on the models of quinidine and 3-hydroxyquinidine by concerted scanning of the C-3'-C-10 (Φ8), C-6'-O-6' (Φ7), C-4'-C-9 (Φ1) and C-9-C-8 (Φ3) rotatable bonds at 5° increments. A set of sterically allowed conformations and estimated relative energies was obtained by this method for each compound. At this point in the modelling study it was determined that quinidine and 3-hydroxyquinidine are virtually identical in conformational behaviour. The modelling studies were therefore continued with quinidine as a model for the conformational preferences of both compounds.

An energy map of the quinidine conformational data set was created by plotting graphs of the allowed Φ1 and Φ3 torsional angles energy contoured at 0.5 kcal mol<sup>-1</sup>† increments. Six local-energy minima were identified by examination of this plot of the quinidine conformational energy surface. The structure of each of the six local-energy minima was refined by another minimization using the MAXIMIN2 force-field. The final structures of the local energy minima are shown in Fig. 4. The Φ1 and Φ3 torsional angles of these six conformations, along with those found in the X-ray crystallographic structures of

\* SYBYL Molecular Modeling System, Tripos Associates, St. Louis, MO.  
† 1 cal = 4.184 J.

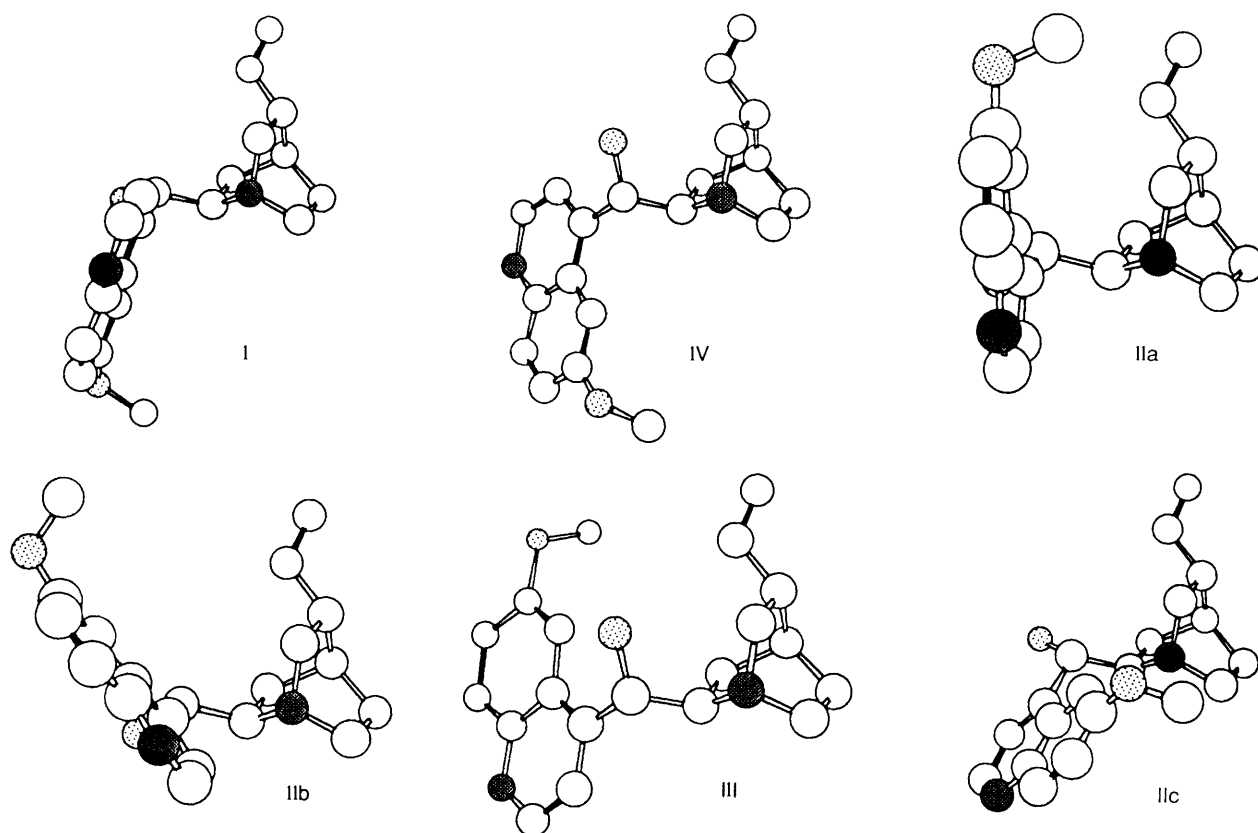


Fig. 4 'Ball and stick' renderings of the six calculated local-energy minima of quinidine. Hydrogen atoms are omitted. Carbon atoms are unshaded, oxygen atoms are shaded light grey and nitrogen atoms are shaded dark grey.

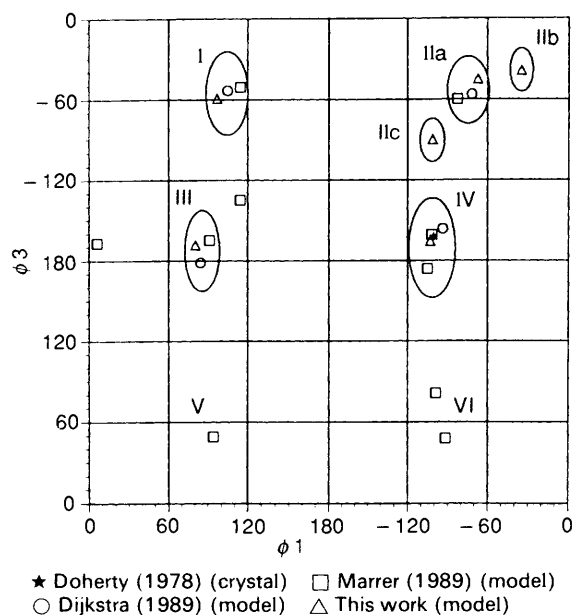


Fig. 5 Quinidine local-energy minima

quinidine and 3-hydroxyquinidine and in other published modelling studies on quinidine, are summarized in Table 5 and displayed in Fig. 5. The vicinity of the six local-energy minima in this Figure are indicated by ovals labelled according to the corresponding quinidine conformational families I–VI (see Fig. 6). The solid-state structures of quinidine and 3-hydroxyquinidine, all four of the Dijkstra conformers,<sup>19</sup> and five of the ten Marrer conformers<sup>21</sup> can be seen to be associated with four of the six conformers identified by this study. Dijkstra's 'quinidine-1' conformer and one of the Marrer conformations

are closely related to the global-energy minimum **1**. Local energy minimum **IV** is very close in structure to both the observed solid-state structures of quinidine and 3-hydroxyquinidine, Dijkstra's global-energy minimum ('quinidine-3') conformer, and two of the Marrer conformations. Dijkstra's 'quinidine-2' and a Marrer conformer are related to conformer **III**, and Dijkstra's 'quinidine-4' and another Marrer conformation are related to conformer **IIa**. The new conformations **IIb** and **IIc**, although relatively close in structure to conformer **II**, were determined to be distinct local-energy minima by the thorough conformational search described above. Neither of these conformers was identified by the Dijkstra or Marrer modelling studies.

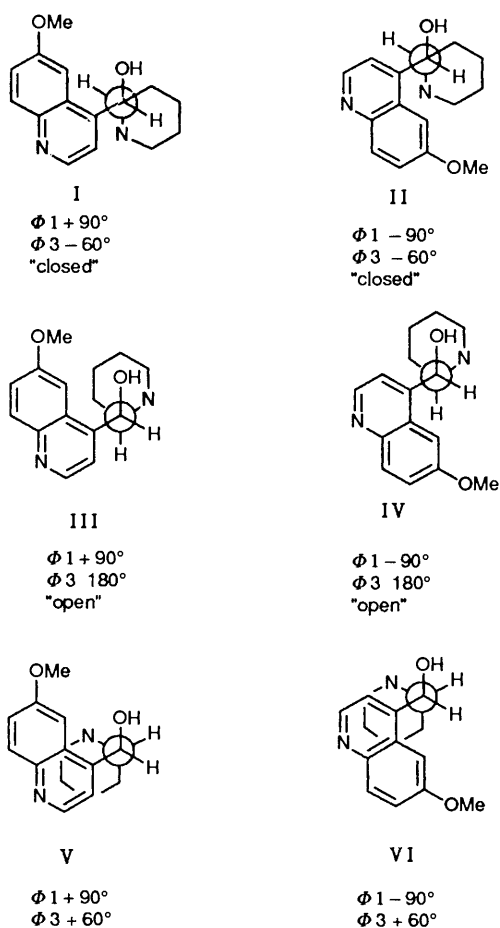
Having established the conformational preference of the central rotatable bonds of quinidine, the torsion of the methoxy group was considered separately. Energy optimizations were performed on multiple starting structures at 5° increments of the methoxy group by using the MM2-87<sup>22</sup> force field and AM1<sup>23</sup> semiempirical quantum mechanics calculations (with full geometry optimization). Four local-energy minima were identified by this method, with  $\Phi_7 = 0^\circ, +90^\circ, 180^\circ$  and  $-90^\circ$ . The  $\Phi_7 \sim 0^\circ$  (*5'* *syn*) and  $\Phi_7 \approx 180^\circ$  (*7'* *syn*) conformations were found to be  $\sim 1.7$  kcal mol<sup>-1</sup> lower in energy than the 90° conformations.

## Discussion

**Structure of Compound 5a.**—In our preliminary report<sup>8</sup> we used a detailed <sup>13</sup>C NMR analysis of the chemical shifts of the C-5 and C-7 methylenes of compounds **1a**, **1b**, **5b** and **6** to assign the stereochemistry at position C-3 of compound **5a**. The chemical shift of C-7 for compound **1b** ( $\delta_C$  24.49) was shifted downfield relative to that in **1a** ( $\delta_C$  23.3), whereas the chemical shift of C-5 in compounds **1a** ( $\delta_C$  26.4) and **1b** ( $\delta_C$  26.1) were essentially identical. The observation that the C-5 and C-7

**Table 5** Local-energy minima of quinidine and 3-hydroxyquinidine: observed and calculated dihedral angles

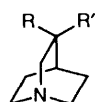
Conformer family	Relative energy	$\Phi 1$	$\Phi 3$	Compound	Data source
IV		-100.6	-162	quinidine	X-ray Ref. 20
IV		-94.9	-157.7	3-hydroxyquinidine	X-ray This work
IV		-93.8	-156.4		
I	0.4	104.5	-53.4	Quinidine	Model Ref. 19
II	0.6	-71.7	-56.6		
III	4	84.4	178.6		
II		-83	-60		
VI	1.5	-92	48		
	1.8	114	-135		
I	1.8	114	-51	Quinidine	Model Ref. 21
VI	1.9	-99	81		
V	2.1	94	49		
IV	3.7	-102	-161		
IV	3.8	-105	174		
III	5.6	91	-165		
	7.6	6	-167	Quinidine	Model This work
I		96.9	-59.1		
IV	0.1	-102.9	-165.6		
IIa	0.3	-66.9	-45.1		
IIb	0.7	-34.7	-38.8		
III	2.3	80.4	-168.3		
IIc	2.5	-101.3	-90		

**Fig. 6** Quinidine conformational families

resonances of compound **5b** ( $\delta_c$  20.34 and 26.15, respectively) showed similar differences in chemical shift relative to compound **5a** ( $\delta_c$  20.6 and 24.7, respectively) suggested that the structure for compound **5a** was that of the 3-*S* isomer. The assignment was supported by comparison of the  $\gamma$ -effect on C-5 and C-7 of compound **5a** and **5b** to model compounds **7a-d**. The chemical-shift assignment of C-5 and C-7 for compounds **1a**, **1b**,

**5a**, **5b**, **6**, and the corresponding positions in **7a-d** used in this analysis, was based on standard  $^{13}\text{C}$  NMR chemical-shift theory<sup>24</sup> and arguments made for other cinchona alkaloids.<sup>17</sup> Thus it was apparent that the structural assignment to compound **5a** is dependent on the correctness of the  $^{13}\text{C}$  NMR assignments. While the assignments were reasonable, we felt that additional evidence was needed to allow us confidently to assign structure **5a** to the major quinidine metabolite. Both  $^1\text{H}$  NMR NOE studies and X-ray crystallographic analysis can provide such information. Initially, the needed evidence was obtained from a detailed NOE study of compound **5a**, a study which also provided some information on the solution conformations of this compound.

The NOEs observed for **5a** maleate in 100% deuterated [ $^2\text{H}_5$ ]pyridine provided convincing evidence that the originally assigned stereochemistry of compound **5a** as (3*S*)-3-hydroxyquinidine is correct. In particular, irradiation of the 5 $\beta$ -proton showed no NOE enhancement of the 10-proton, whereas irradiation of the 7 $\beta$ -proton gave an 11% enhancement of the 10-proton. In addition, irradiation of the 10-proton showed a 6% enhancement of the 7 $\beta$ -proton with no enhancement of the 5 $\beta$ -proton. The smaller enhancement (6%) for the 7 $\beta$ -proton is expected since the NOE for a hydrogen is dependent upon all possible relaxation processes and the 7 $\beta$ -proton has stronger relaxation pathways (*i.e.*, 7 $\beta$ -H and 7 $\alpha$ -H) than does the 10-proton.<sup>18</sup> Owing to the rigid nature of the quinuclidine rings, these NOE results require that the 7 $\beta$ -proton and 3-vinyl substituent be on the same side of the quinuclidine ring. Therefore the observed NOEs for the 7 $\beta$ - and 5 $\beta$ -proton with the 10-proton are uniquely consistent with the (3*S*)-3-hydroxyquinidine structure **5a** as the major metabolite of quinidine. Furthermore, the structure and absolute stereochemistry of compound **5a** were unambiguously established by single-crystal X-ray analysis. The final co-ordinates are given in Table 6, and the structure is depicted in Fig. 3. Hence, the microbial oxidation of quinidine takes place with retention of configuration, *i.e.* the original hydrogen is 'replaced' by the hydroxy group, in agreement with previous reports of the microbial oxidation of quinidine<sup>25</sup> and in agreement with literature references which indicate preferential retention for such transformations.<sup>25,27</sup> At the same time, this confirms the structure of the (3*S*)-3-hydroxydihydroquinidine, which can be prepared by microbial oxidation of dihydroquinidine, and has been linked chemically to the corresponding



- 7a: R' = H, R = H  
 b: R' = OH, R = H  
 c: R' = H, R' = CH=CH<sub>2</sub>  
 d: R' = OH, R' = CH=CH<sub>2</sub>

Quinidine model compounds

**Table 6** Fractional atomic co-ordinates ( $\times 10^4$ ) for non-hydrogen atoms with estimated standard deviations in parentheses for compound **5a** methanesulphonate. (Parameter marked by an asterisk was not varied.)

	<i>x</i>	<i>y</i>	<i>z</i>
C(1)	8 148(8)	8 124(8)	7 502(7)
C(2)	8 046(7)	7 743(9)	6 232(7)
N(3)	6 962(6)	7 111(8)	5 326(6)
C(4)	5 849(7)	6 854(7)	5 699(7)
C(5)	4 707(8)	6 110(8)	4 773(7)
C(6)	3 561(8)	5 852(8)	5 057(7)
C(7)	3 448(7)	6 289(8)	6 249(8)
C(8)	4 548(7)	6 972(8)	7 199(7)
C(9)	5 776(8)	7 248(7)	6 936(7)
C(10)	6 988(7)	7 895(8)	7 864(7)
O(11)	2 203(5)	6 017(6)	6 382(5)
C(12)	2 028(9)	6 499(9)	7 577(9)
C(13)	7 077(8)	8 262(8)	9 271(7)
O(14)	8 024(6)	9 308(6)	9 855(6)
C(15)	7 524(8)	7 040(9)	10 149(7)
C(16)	9 115(7)	6 741(8)	10 658(8)
C(17)	9 643(8)	6 330(8)	12 131(8)
C(18)	9 560(7)	7 471(8)	13 042(7)
C(19)	8 044(8)	8 015(9)	12 416(8)
N(20)	7 114(6)	7 097(7)	11 368(6)
C(21)	7 226(9)	5 742(8)	11 969(8)
C(22)	8 686(8)	5 201(8)	12 240(8)
C(23)	10 610(8)	8 540(8)	13 146(8)
C(24)	11 480(9)	9 038(9)	14 307(9)
O(25)	9 700(5)	6 979(6)	14 334(5)
S(26)	3 485(2)	7 728(*)	1 022(2)
O(27)	4 448(5)	8 156(6)	383(5)
O(28)	2 036(5)	8 053(7)	261(5)
O(29)	3 705(6)	6 337(6)	1 387(5)
C(30)	4 008(11)	8 587(10)	2 548(10)

quinidine **5a** in that the latter can be hydrogenated to give the identical 3-hydroxydihydroquinidine.<sup>27,\*</sup>

**Conformation of Compounds 1a and 5a.**—The overall conformation of cinchona alkaloids is determined by the quinoline-to-C-9 dihedral angle ( $\Phi 1$ ) and the quinuclidine-to-C-9 dihedral angle ( $\Phi 3$ ). These two torsions determine the geometric relationship between the rigid quinoline and quinuclidine ring systems. Conformations with  $\Phi 1 = +90^\circ$  or  $-90^\circ$  are expected to be lowest in energy, as first pointed out by Prelog<sup>28</sup> and Meurliq,<sup>29</sup> since these two dihedral angles place the bulky quinuclidine in a less sterically demanding region perpendicular to the planar quinoline ring. The second dihedral should adopt an angle near one or more of the three possible staggered conformations with  $\Phi 3 = -60^\circ$ ,  $180^\circ$  or  $+60^\circ$ . Two of these

three conformations should be accessible ( $\Phi 3 = -60^\circ$  or  $180^\circ$ ). Dijkstra *et al.*<sup>19,30</sup> have termed these alternatives the 'open' ( $\Phi 3 \approx 180^\circ$ ) and 'closed' ( $\Phi 3 \approx -60^\circ$ ) conformations. The third conformation ( $\Phi 3 \approx +60^\circ$ ) would be expected to be highly unstable as two large groups would be in a sterically unfavourable eclipsed relationship. Newman projections of the six theoretically possible quinidine conformational families are illustrated in Fig. 6.

It is interesting to compare the conformation of **5a** methanesulphonate observed in both the solid state and solution with results found in the literature for other quinidine derivatives. Compound **5a** methanesulphonate is in 'open' conformation **IV** (Fig. 4) with  $\Phi 1 -94.4^\circ$  and  $\Phi 3 -157.7^\circ$ . Similar 'open' conformations are found in the solid state for quinidine,<sup>31</sup> quinidine ethanolate,<sup>20</sup> (10*R*)-10,11-dihydroxy-10,11-dihydroquinidine,<sup>32</sup> cinchonium cation,<sup>33</sup> 10-hydroxy-10-methyl-10,11-dihydroquinidine, and quinidinium  $\Delta(-)_{5,4,6}$ -bis(oxalato)(1,10-phenanthroline)chromate(III) monohydrate.<sup>34</sup> A similar 'open' conformation is found in solution by use of NMR techniques.<sup>19,30,35</sup> In general, the 'open' conformation is preferred for all free bases with a C-9-hydroxy group, as well as for all protonated or complexed forms.<sup>19,30</sup> The close analogy between the conformations found in the solid state and in solution indicates that intramolecular forces predominate in determining the overall conformation of cinchona alkaloids, rather than solid-state or solvent interactions.<sup>31</sup> The 6'-methoxy group in the X-ray crystallographic structure is essentially in the 5'-*syn* conformation, coplanar with the quinoline ring (see Table 4,  $\Phi 7$ ).

A comparison of the various molecular modelling studies with the observed structures is also instructive. Dijkstra and co-workers found four conformations for dihydroquinidine using a grid search and the MM2-87 and MMX force fields. These conformations correspond to the four theoretically most likely conformations **I-IV** (Fig. 5). Three of the four Dijkstra conformations are relatively close in energy (within 1 kcal mol<sup>-1</sup>) with the global-energy minimum calculated to be very close to conformation **IV**, the same conformation found in the solid state. Marrer, on the other hand, identified ten possible local-energy-minimum conformations over a range of 7.6 kcal mol<sup>-1</sup> above the global-energy-minimum conformation.<sup>21</sup> The global-energy-minimum conformation found by this worker was related to the 'closed' conformation **II**, with the lowest energy 'open' conformation (**IV**) 3.7 kcal mol<sup>-1</sup> above the global-energy minimum.

Although the strongly coupled motions of the central  $\Phi 1$  and  $\Phi 3$  rotatable bonds determine the overall conformation of quinidine, the possibility exists that these rotations may be perturbed somewhat by interaction with the methoxy and vinyl groups. This question was examined by performing systematic conformational searches while varying all four rotatable bonds. Previously published conformational searches have apparently been performed with fixed vinyl and methoxy groups. As in the Dijkstra modelling study, conformations belonging to the four theoretically most likely conformation families **I-IV** were identified as viable local-energy minima. Mapping the conformation space of quinidine at 5° resolution and 0.5 kcal mol<sup>-1</sup> energy contours suggested the existence of a total of three local-energy minima related to conformer family **II** (**IIa**, **IIb** and **IIc** in Fig. 5 and Table 5). These distinct local-energy minima apparently arise from interactions of the quinidine 3'- and 5'-protons with the quinuclidine C-9 and C-2 protons. The global-energy minimum identified using the MAXIMIN2 force field was related to the 'closed' conformation **I**, calculated to be only 0.1 kcal mol<sup>-1</sup> lower in energy than the 'open' conformer observed in the solid state, **IV**. These results do not suggest a strong *steric* preference for either conformation although electrostatic (dipole-dipole) or matrix effects may account for the observed preference for conformer **IV**.

\* It should be noted that both quinidine and dihydroquinidine possess the (3*R*)-configuration. On replacing the 3-H with the 3-OH group (with retention) the configuration according to the Cahn-Ingold-Prelog rules changes to (3*S*) for both compounds. A number of references in the literature (and corresponding reporting in Chemical Abstracts) to (3*R*)-hydroxydihydroquinidine and other derivatives appear to be erroneous.

**Table 7** Selected inter-ring proton-proton distances (Å) (from the six calculated local-energy minima of quinidine)

	3'-2 $\alpha$	3'-7 $\beta$	3'-9	5'-2 $\alpha$	5'-8	5'-10
<b>I</b>	2.472	4.768	2.388	5.561	2.401	6.100
<b>IV</b>	4.634	2.678	3.611	4.993	2.460	6.250
<b>IIa</b>	4.866	4.843	3.732	2.472	4.786	3.148
<b>IIb</b>	4.105	4.845	3.767	3.665	4.909	3.831
<b>III</b>	5.401	4.659	2.398	3.978	4.335	2.591
<b>IIc</b>	5.680	4.319	3.587	2.601	3.540	4.689

An examination of the NOE data acquired for 3-hydroxyquinidine was undertaken to determine which of the predicted conformations of quinidine system can be detected in solutions of this compound. Inter-ring proton-proton NOE enhancements were detected for proton pairs 3'-2 *syn*, 3'-7 $\beta$ , 3'-9, 5'-2 *syn*, 5'-8 and 5'-10. The distances between these protons in each of the predicted local energy minimum conformations is shown in Table 7. Each of these pairs of protons is brought into suitable proximity in the predicted local-energy-minimum conformations to account for the observed enhancements. Conformation **I** accounts uniquely for the NOE between protons 3'-H and 2' *syn*. Likewise, the existence of conformations **III** and **IV** in solution is strongly supported by the 5'-10 and 3'-7 $\beta$  enhancements. An NOE between 3'- and 8-protons that would have verified the existence of any of the family (species **II**) of conformations was not observed.

Molecular mechanics and semiempirical quantum mechanics calculations with full geometry optimization showed local minimum-energy conformations for the methoxy group at  $\Phi 7 \approx 0^\circ$ ,  $+90^\circ$ ,  $180^\circ$  and  $-90^\circ$ . The  $\Phi 7 \approx 0^\circ$  (5' *syn*) and  $\Phi 7 \approx 180^\circ$  (7' *syn*) conformations (methoxy group in the plane of the quinoline ring) are found to be  $\sim 1.7$  kcal mol $^{-1}$  lower in energy by both semiempirical calculations (AM1) and the Allinger (MM2-87) force field. Force-field calculations based only on steric contributions yield lower energies for conformations with the methoxy group orthogonal to the quinoline ring. 5'-*syn* conformation is generally observed to be the favoured conformation in the solid-state and solution.

The vinyl group is expected to point away from the centre of the quinuclidine ring system and nitrogen atom in the most stable conformation with a dihedral angle  $\Phi 8$  of 100–180°. The angle observed for **5a** methanesulphonate is 111.6°. The corresponding values observed in the solid state are 109.6° for quinidine,<sup>31</sup> 123° for quinidine ethanolate<sup>19</sup> and 18° for quinidine (-)-1,1'-dimethylferrocene-3-carboxylic acid salt.<sup>36</sup> In solution, NMR data showed a similar conformation for the vinyl group of quinidine.<sup>35</sup>

The quinuclidine ring system is expected to twist somewhat to relieve the strain from the various eclipsed interactions. The X-ray structure shows a right-handed twist to give values for the dihedral angles of  $\sim +12 - 13^\circ$  for the connecting chains N-1-C-C-4 (see Table 1,  $\Phi 9$ - $\Phi 11$ ). (A right-handed twist corresponds to a positive value for the corresponding N-1-C-C-4 dihedral angle.) Most, if not all, cinchona alkaloids and derivatives possessing the quinidine configuration at C-8 seem to prefer the right-handed twist, as evidenced by X-ray diffraction studies and NMR data.<sup>19,30</sup>

Finally, it is tempting to speculate on which conformation of quinidine and (3*S*)-3-hydroxyquinidine is the active one at the receptor on the sodium channel and thus responsible for the antiarrhythmic activity. Generally, it is accepted that the active form of quinidine is the protonated form.<sup>37</sup> (The same holds true for most other antiarrhythmic agents.) Clearly, the preferred conformation for quinidine and (3*S*)-3-hydroxyquinidine is related to conformer family **IV** with values of  $\sim -90^\circ$  for  $\Phi 1$  and  $\sim -160^\circ$  for  $\Phi 3$ . The latter corresponds to an O-C-9-C-8-N-1 angle of  $\sim 80^\circ$ . However, other conformations are also

energetically accessible,<sup>19,21,30</sup> and thus it cannot be excluded *a priori* that another conformation represents the active one bound to the receptor. Marrer has suggested, based upon comparing quinidine with the antiarrhythmics lidocaine and EO-122 *via* molecular modelling, an active conformation defined by  $\Phi 1$  and  $\Phi 3$  dihedral angles of  $+114^\circ$  and  $-51^\circ$ , respectively.<sup>21</sup> This corresponds to a type-**II** quinidine conformation. However, this conformation does not seem to have been observed so far either in the solid state or in solution. (A 'closed' conformation of type **I** has been found by Dijkstra for (*p*-chlorobenzoyl)dihydroquinidine where  $\Phi 1 \approx -90^\circ$ ).<sup>19,30</sup>

## Experimental

**Synthesis.**—M.p.s were determined on a Thomas-Hoover capillary-type apparatus or a Kofler hot stage and are uncorrected.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker WM-500 spectrometer. IR spectra were recorded on a Perkin-Elmer Model 267 grating spectrophotometer. All optical rotations were recorded at the sodium D line with a Perkin-Elmer Model 141 polarimeter (1-dm cell). Microanalyses were carried out by Micro-Tech Laboratories, Skokie, IL.

**Apoquinidine Methyl Ether 3a.**—A. From pure  $\alpha$ -10-Bromodihydroquinidine. A stirred mixture of  $\alpha$ -10-bromodihydroquinidine **2** (6.74 g, 0.017 mol) (isolated in 10% yield by hydrobromination of quinidine),<sup>9</sup> DBU (2.79 g, 0.018 mol) and dry DMSO (80 cm $^3$ ) was heated at 85–90 °C for 2 h. The cooled reaction mixture was diluted with water and extracted with methylene dichloride. The extracts were dried (Na $_2$ SO $_4$ ), and concentrated under reduced pressure. The residue was recrystallized from diethyl ether-hexane to give apoquinidine methyl ether **3a** (4.25 g, 79%), m.p. 178–180 °C (lit.,<sup>9</sup> 180–181 °C). An analytical sample recrystallized from aq. acetone had m.p. 85–95 °C;  $\delta_{\text{H}}(\text{CDCl}_3)$  1.51 (d, MeCH), 3.94 (s, MeO), 5.20 (q, =CHMe) and 5.58 (d, CHOH);  $[\alpha]_{\text{D}}^{25} + 178.25^\circ$  (*c* 0.40, EtOH) (lit.,<sup>9</sup> m.p. 90–100 °C);  $[\alpha]_{\text{D}}^{25} + 193.2^\circ$  (Found: C, 73.7; H, 7.4; N, 8.65. Calc. for C $_{20}$ H $_{24}$ N $_2$ O $_2$ : C, 74.04; H, 7.46; N, 8.64%).

B. From crude  $\alpha$ - and  $\alpha'$ -Bromodihydroquinidine **2**. A solution of quinidine (5.0 g, 0.015 mol) in 48% hydrobromic acid (15 cm $^3$ ) was saturated with hydrogen bromide at 0 °C and stirred at this temperature for 1 h and then at 25 °C for 1 h. The reaction mixture was cooled again to 0 °C and neutralized, 50% aq. sodium hydroxide and extracted with chloroform. The extracts were washed (water), dried (Na $_2$ SO $_4$ ), and concentrated under reduced pressure to give crude bromo compound **2**.

A solution of the crude bromo mixture **2** and DBU (2.79 g, 0.018 mol) in dry DMSO (18 cm $^3$ ) was heated at 85–90 °C for 2 h. The cooled reaction mixture was diluted with water and extracted with methylene dichloride. The extracts were dried (Na $_2$ SO $_4$ ), and concentrated under reduced pressure. The residue was recrystallized from diethyl ether-hexane to give apoquinidine methyl ether **3a** (3.25 g, 65%), m.p. 178–180 °C (lit.,<sup>9</sup> 180–181 °C).

**Apoquinidine Methyl Ether 9-Acetate 3b.**—A solution of apoquinidine methyl ether **3a** (4.2 g, 0.013 mol) in pyridine (30 cm $^3$ )-acetic anhydride (30 cm $^3$ ) was stirred at 25 °C for 16 h. The reaction mixture was diluted with water, made alkaline with conc. ammonium hydroxide, and extracted with methylene dichloride. The residue obtained was dried under high vacuum and was then recrystallized from diethyl ether-hexane to give the *title compound* (3.89 g, 82%), m.p. 110–112 °C;  $\nu_{\text{max}}(\text{CS}_2)/\text{cm}^{-1}$  1724 (acetate C=O);  $\delta_{\text{H}}(\text{CDCl}_3)$  1.52 (d, MeCH), 2.07 (s, MeCO), 3.94 (s, MeO), 5.22 (m, =CHMe) and 6.48 (d, CHOAc);  $[\alpha]_{\text{D}}^{24} + 61.09^\circ$  (*c* 0.568, EtOH) (Found: C, 72.2; H, 7.4; N, 7.8. C $_{22}$ H $_{26}$ N $_2$ O $_3$  requires C, 72.10; H, 7.15; N, 7.65%).



(8R,9S)-6'-Methoxy-3-oxoruban-9-yl Acetate **4**.—A mixture of apoquinidine methyl ether 9-acetate **3b** (2.5 g, 0.0068 mol) osmium tetroxide (0.63 g) in 80% acetic acid (20 cm<sup>3</sup>) was stirred at 25 °C for 3 h. The reaction mixture was cooled to 4 °C, powdered sodium metaperiodate (1 g) was added, and the mixture was stirred continually for 16 h and then was filtered, and the solids obtained were washed with acetic acid. The combined filtrate and washings were concentrated under reduced pressure. The resulting residue was dissolved in water, treated with an excess of aq. sodium hydrogen carbonate, and extracted with chloroform. The dried (Na<sub>2</sub>SO<sub>4</sub>) extracts were concentrated to small volume and chromatographed on a Florisil column with chloroform–ethyl acetate (60:40) as the eluent. The product fractions were concentrated and the solid obtained was recrystallized from acetone–diethyl ether mixture to give the *title compound* (1.8 g, 75%), m.p. 162–163 °C;  $\nu_{\max}(\text{CS}_2)/\text{cm}^{-1}$  1735 (ketone C=O) and 1742 (acetate C=O);  $\delta_{\text{H}}(\text{CDCl}_3)$  2.14 (s, MeCO), 3.95 (s, MeO) and 6.53 (d, CHOAc);  $[\alpha]_{\text{D}}^{25} + 58.46^\circ$  (*c* 0.40, EtOH) (Found: C, 68.0; H, 6.4; N, 8.0. C<sub>20</sub>H<sub>22</sub>N<sub>2</sub>O<sub>4</sub> requires C, 67.78; H, 6.26; N, 7.91%).

(3S)-3-Hydroxyquinidine **5a** and (3R)-3-Hydroxyquinidine **6**.—To a stirred solution of a 1.98 mol dm<sup>-3</sup> solution of vinylmagnesium chloride in THF (15.2 cm<sup>3</sup>) under nitrogen at 0 °C was added a solution of compound **4** (2.67 g, 7.5 mmol) in dry THF (10 cm<sup>3</sup>). The reaction mixture was stirred at 0 °C for an additional 45 min and was then quenched with 6 mol dm<sup>-3</sup> hydrochloric acid. The mixture was made alkaline with 7 mol dm<sup>-1</sup> ammonium hydroxide and extracted with methylene dichloride. The extracts were concentrated, and the resulting oil was treated with 5% alcoholic potassium hydroxide for 1 h, diluted with water, and again extracted with methylene dichloride. The dried (Na<sub>2</sub>SO<sub>4</sub>) extracts were concentrated under reduced pressure to give an oil, which was chromatographed on Florisil with a methylene dichloride–methanol gradient as the eluent. The first component eluted was (3R)-3-hydroxyquinidine **6** (0.915 g, 32%). A sample recrystallized from ethyl acetate had m.p. 188–190 °C;  $[\alpha]_{\text{D}}^{25} + 132.42^\circ$  (*c* 0.91, EtOH) (Found: C, 68.9; H, 7.1; N, 7.95. C<sub>20</sub>H<sub>24</sub>N<sub>2</sub>O<sub>3</sub>·0.5 H<sub>2</sub>O requires C, 68.75; H, 7.20; N, 8.00%).

The second component eluted from the column was (3S)-3-hydroxyquinidine **5a** (1.38 g, 48%). A sample recrystallized from methyl acetate had m.p. 204–206 °C;  $[\alpha]_{\text{D}}^{25} + 248.52^\circ$  (*c* 0.54 g, MeOH) (lit.,<sup>13</sup> m.p. 211–212 °C).

The maleate salt had m.p. 225–226 °C,  $[\alpha]_{\text{D}}^{25} + 190.55^\circ$  (*c* 0.54 g, MeOH) (lit.,<sup>8</sup> m.p. 225–226 °C).

(3S)-3-Hydroxyquinidine 9-Benzoate **5b**.—A solution of (3S)-3-hydroxyquinidine (50 mg) in pyridine (5 cm<sup>3</sup>) containing benzoic anhydride (35 mg) was stirred at 40–50 °C for 25 h. The cooled reaction mixture was diluted with water, made alkaline with aq. ammonium hydroxide, and extracted with methylene dichloride. The dried (K<sub>2</sub>CO<sub>3</sub>) extracts were concentrated under reduced pressure and the residue was recrystallized from acetone–hexane to give monobenzoate **5b**, m.p. 185–186 °C. An analytical sample recrystallized from the same solvent mixture had m.p. 188–189 °C (Found: C, 72.8; H, 6.5; N, 6.15. C<sub>27</sub>H<sub>28</sub>N<sub>2</sub>O<sub>4</sub> requires C, 72.95; H, 6.35; N, 6.30%).

*Preparation of (3S)-3-Hydroxyquinidine 5a by Microbial Oxidation of Quinidine*.—A 2-dm<sup>3</sup> Erlenmeyer flask containing a nutrient solution (500 cm<sup>3</sup>) made up of 3% glucose, 1% corn steep liquor, 0.2% NaNO<sub>3</sub>, 0.1% KH<sub>2</sub>PO<sub>4</sub>, 0.2% K<sub>2</sub>HPO<sub>4</sub>, 0.05% MgSO<sub>4</sub>·7 H<sub>2</sub>O, 0.002% FeSO<sub>4</sub>·7 H<sub>2</sub>O and 0.05% KCl and sterilized in an autoclave for 30 min at 120 °C, was inoculated with a 7-day-old slanted-tube culture of the strain *Cunninghamella verticillata* (ATCC 8983) and was shaken for 2.5 days on a rotary shaker. Six of these germination cultures

were used to inoculate a 75-dm<sup>3</sup> steel fermentor filled with a medium (47 dm<sup>3</sup>) having the same composition as the germination cultures, and germination was carried out under aeration (15 dm<sup>3</sup> min<sup>-1</sup>) and agitation (200 rpm) at 29 °C. After an incubation period of 12 h, the substrate was added as a solution of quinidine (25 g) in dimethylformamide (250 cm<sup>3</sup>), and fermentation was continued for 264 h. The culture was filtered and basified, and the solution was extracted with isobutyl methyl ketone. The organic phase was evaporated under reduced pressure, and the residue was chromatographed twice on a silica gel column with gradient elution (5 dm<sup>3</sup> methylene dichloride/4.5 dm<sup>3</sup> methylene dichloride + 0.5 dm<sup>3</sup> methanol). The fraction containing the (3S)-3-hydroxyquinidine was recrystallized from acetone to yield a first crop of 145 mg, m.p. 201–204 °C. The compound was identical with the sample synthesized in the previous experiment.

*NMR Experiments*.—All NMR experiments were carried out on either a modified Bruker WM-250 MHz instrument with an Aspec-3000 computer with array and graphics display processors or a Bruker AMX-500 MHz NMR with a 32532 coprocessor. All spectra were obtained by using a 5 mm switchable <sup>1</sup>H/<sup>13</sup>C probe using SiMe<sub>4</sub> as reference at 0.0 ppm at 300 K. The 2D proton correlation experiment used was the COSY-45 experiment described by Ernst<sup>14,15</sup> using a 2 K data size with one zero-fill in the *F1* dimension and a shifted sine bell weighted function for both dimensions. The 2D proton–carbon correlation was obtained by using the HETCOR experiment described by Bax,<sup>16</sup> with a *J*<sub>CH</sub>-value of 140 Hz with a 2 K data size and one zero-fill in *F1*. A shifted sine bell squared weighting function was used in both dimensions.

NOE data were obtained on a 5 mg sample of the maleate salt of the product dissolved in 100% [<sup>2</sup>H<sub>5</sub>]pyridine. The sample was placed in an NMR tube, degassed, and sealed under vacuum. The NOE experiment was run with a 3 s relaxation delay at various decoupling powers to obtain maximum NOE suppression. At optimum decoupler power a series of NOE experiments were run with various relaxation delays to obtain the most reproducible data. The experiment was then run using an NOEDIFF automation program with optimum decoupler power and relaxation delay. The reference spectrum was run under the same conditions with decoupling at an off-peak reference at 10 ppm. Three separate sets of experimental data were acquired with 320 transients each. Each integral value was compared with the reference and the difference was determined. The values for the three experiments were then averaged. NOE difference data were confirmed by using a 2D-NOESY experiment at 500 MHz.

*Single-crystal X-Ray Structure Determination of (3S)-3-Hydroxyquinidine Methanesulphonate (1:1)*.—Solutions of (3S)-3-Hydroxyquinidine (20 mg, 0.059 mmol) in acetone (3 cm<sup>3</sup>) and 0.58 mol dm<sup>-3</sup> methanesulphonic acid in acetone (0.1 cm<sup>3</sup>; 0.058 mmol) were combined and heated gently to complete dissolution. Slow crystallization resulted in large crystals, m.p. 207–209 °C, suitable for X-ray structure determination;  $\delta_{\text{H}}([\text{}^2\text{H}_6\text{]DMSO})$  1.30 (1 H, m), 1.58 (1 H, m), 1.91 (1 H, m), 2.09 (2 H, m), 2.32 (3 H, s), 2.9–3.6 (3 H, m), 3.7–4.4 (3 H, m), 3.97 (3 H, s), 5.28 (1 H, d), 5.43 (1 H, d), 5.90 (1 H, br), 6.21 (1 H, dd), 6.47 (1 H, br), 7.36 (1 H, s), 7.45 (1 H, d), 7.58 (1 H, d), 8.00 (1 H, d), 8.75 (1 H, d) and 10.26 (1 H, br).

*Crystal data*. C<sub>20</sub>H<sub>24</sub>N<sub>2</sub>O<sub>3</sub>·MeSO<sub>3</sub>H, *M* = 436.52. Monoclinic, *a* = 10.248(3), *b* = 10.209(3), *c* = 10.741(3) Å,  $\beta$  = 112.28(1)°, *V* = 1039.86 Å<sup>3</sup>, *T* = 118 K, Mo-*K* $\alpha$  radiation,  $\lambda$  = 0.710 69 Å, space group *P2*<sub>1</sub>, *D*<sub>m</sub> = 1.394 174, *Z* = 2, *D*<sub>x</sub> = 1.394 g cm<sup>-3</sup>. Crystal dimensions 0.25 × 0.25 × 0.25 mm,  $\mu(\text{Mo-}K\alpha) = 1.872 \text{ cm}^{-1}$ .

*Data collection and processing*. A computer-controlled Picker

four-circle goniostat equipped with a Furnas Monochromator (HOG crystal) and Picker X-ray generator (Mo-K $\alpha$  radiation,  $\lambda = 0.71069 \text{ \AA}$ ) was employed in the study and the sample was cooled to  $-155^\circ\text{C}$ . A total of 1444 unique intensities were measured with  $6^\circ \leq 2\theta \leq 45^\circ$ . Of these, 1292 were observed ( $F > 2.336 \sigma(F)$ ) and corrected for Lorentz and polarization effects.

**Structure analysis and refinement.** The structure was solved by using the MULTAN 18 interactive crystallographic program, and was refined by using full-matrix least-squares. The function minimized was  $\sum \omega(|F_o| - |F_c|)^2$  with  $\omega = 1/(\sigma F)^2$  to give an unweighted residual value  $R(F)$  of 0.0466 and a weighted value of 0.0464.

The refined fractional co-ordinates are shown in Table 6, and the resulting molecular structure is illustrated in Fig. 3.\*

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\* *Supplementary data* (see section 5.6.3 of Instructions for Authors, January issue). Tables of final atomic co-ordinates, isotropic and anisotropic thermal parameters, bond lengths and bond angles have been deposited at the Cambridge Crystallographic Data Centre.

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