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The Structures of Kidamycin Derivatives: Triacetylmethoxykidamycin Bis(trimethylammonium) Iodide and Isokidamycin Bis(*m*-bromobenzoate)

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Abstract

Two derivatives of kidamycin, an antitumor antibiotic isolated from the metabolite of a *Streptomyces* species, have been studied by X-ray diffraction. Triacetylmethoxykidamycin bis(trimethylammonium) iodide (I), $C_{48}H_{64}N_2O_{13}^{2+}.2I^-.4CH_4O.H_2O$, a methanolysis product of kidamycin, crystallized from a methanol–ethyl acetate solution in $P2_12_12_1$ with lattice constants a = 15·56 (1), b = 39·49 (2), c = 10·182 (7) Å, Z = 4. Isokidamycin bis(*m*-bromobenzoate) (II), $C_{53}H_{54}Br_2N_2O_{11}.0{\cdot}5C_6H_6$, a heavy-atom derivative of the stable isomerized product of kidamycin in protic solvents, crystallized from a benzene–acetone–*n*-hexane solution as an orthorhombic crystal, $P2_12_12_1$, with a = 19·270 (9), b = 41·34 (2), c = 13·933 (7) Å, Z = 8. Both crystal structures were solved by the heavy-atom method but in the case of (II) the diffraction data from the bis(*m*-iodobenzoate) derivative were also utilized in the initial stages. The refinement was carried out by the block-diagonal least-squares method to R values 0·125 for (I) and 0·113 for (II). The skeleton of kidamycin is a tetracyclic anthraceno[1,2-*b*]pyran system and the two tetrahydropyran rings are linked through C-glycosidic bonds. The compounds constitute a new class of polycyclic microbial metabolites. The reaction mechanisms of the methanolysis as well as the isomerization are proposed on the basis of the structures.

Introduction

Kidamycin is an antitumor antibiotic isolated from the metabolite of *Streptomyces phaeoverticillatus* (Kanda, 1971, 1972). Extensive studies have been carried out to elucidate the chemical structure and to modify it in order to diminish undesirable side effects in therapeutical use (Furukawa, Hayakawa, Ohta & Iitaka, 1975). We have found that kidamycin is sensitive to light and protic solvents, and under weakly acidic conditions it is converted into a more stable isomer, isokidamycin. However, the IR, UV and mass spectra of kidamycin and isokidamycin were indistinguishable from each other. Only slight

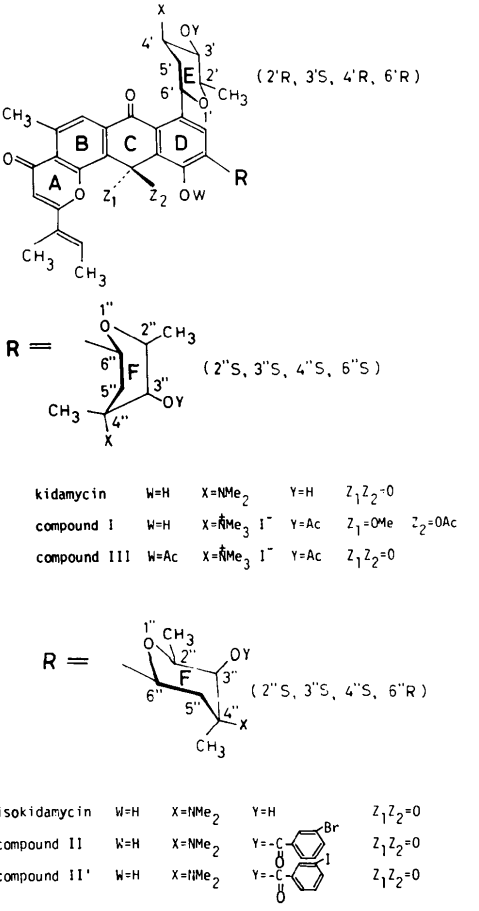

Fig. 1. Chemical structures of kidamycin, isokidamycin and related compounds.

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differences were observed in their NMR spectra and specific rotations. The reduced biological activity of isokidamycin prompted us to elucidate the isomerization mechanism of kidamycin by which a certain functional group essential for the biological activity must be destroyed. Since kidamycin seemed to have a new type of structure, X-ray structural studies on kidamycin and isokidamycin have been carried out parallel to chemical and spectroscopic studies.

A preliminary report of the structure of the methanolysis product of a kidamycin derivative, triacetylmethoxykidamycin bis(trimethylammonium) iodide (I) (Furukawa, Itai & Iitaka, 1973) and the structure of an isokidamycin derivative, isokidamycin bis(*m*-bromobenzoate) (II) (Furukawa & Iitaka, 1974), and a full account of the chemical study (Furukawa, Hayakawa, Ohta & Iitaka, 1975) have been published. The chemical structures of kidamycin and isokidamycin are shown in Fig. 1.

Experimental

Of about twenty heavy-atom derivatives of kidamycin prepared by chemical modifications, only three were found to be suitable for X-ray diffraction study: (I), (II) and isokidamycin bis(*m*-iodobenzoate) (II′).

Crystals of (I) were grown from a methanol–ethyl acetate solution of triacetylkidamycin bis(trimethylammonium) iodide (III). After several months, large crystals of (I), a methanolysis product of (III), were formed in the solution together with crystals of (III). A preliminary X-ray study of (III) showed that the space group is $P1$ with four molecules in a unit cell; analysis of the structure proved difficult.

Our first analysis was therefore carried out for (I). The intensities were measured for 1415 Friedel pairs and the averages $[|F(hkl)| + |F(h\bar{k}\bar{l})|]/2$, were used.

For the structure determination of isokidamycin, crystals of two analogous compounds (II) and (II′) were used. The lattice constants [$a = 19{\cdot}39$, $b = 41{\cdot}70$, $c = 14{\cdot}02$ Å for (II′)] and space group [$P2_12_12_1$ for both (II) and (II′)] showed that they are isomorphous. The intensities of 3033 reflections for (II) and 1546 Friedel pairs of (II′) were measured. The crystal data and the method of intensity measurement are summarized in Table 1.

Structure determination

The structure of (I) was solved by the heavy-atom method. The phase-angle determination by the

Table 1. *Crystal, intensity-measurement and structure-determination data*

	(I) Triacetylmethoxykidamycin bis(trimethylammonium) iodide $C_{48}H_{64}N_2O_{13}^{2+}.2I^-.4CH_3OH.H_2O$	(II) Isokidamycin bis(*m*-bromobenzoate) $C_{53}H_{54}Br_2N_2O_{11}.0{\cdot}5C_6H_6$
Crystallization solvent	Methanol–ethyl acetate	Benzene–acetone–*n*-hexane
Crystal nature	Pale-yellow prism, elongated along *c*, efflorescent	Red prism, elongated along *c*
Formula weight	1277·0	1093·9
Crystal system	Orthorhombic	Orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$
Z	4	8
D_x	1·356 Mg m^{-3}	1·309 Mg m^{-3}
D_m	1·360	1·307
a	15·56 (1) Å	19·270 (9) Å
b	39·49 (2)	41·34 (2)
c	10·182 (7)	13·933 (7)
U	6256·48 (5) Å^3	11099·33 (4) Å^3
Radiation	Cu $K\alpha$, Ni-filtered	Cu $K\alpha$, graphite-monochromated
Crystal size	0·2 × 0·07 × 0·7 mm*	0·2 × 0·07 × 0·5 mm
μ for Cu $K\alpha$	9·90 mm^{-1}	2·59 mm^{-1}
2θ range	0–80°	0–100°
Scan, number of scans	θ–2θ, 1	θ–2θ, 2 when total counts <1000
Scan speed, scan range	2θ 2° min^{-1}, 0–80°	2θ 4° min^{-1}, 0–100°
Slit	1·5° circular	Horizontal 1°, vertical 1·5°
Background measurement	10 s at each end of scan	Scan time/2 at each end of scan
Number of independent observed reflections	1415	3033
Observed ratio†	0·53	0·50
Temperature factor‡	9·6 Å^2	4·7 Å^2
Final R value	0·125	0·113
Anisotropic temperature factors	For all atoms except H	For all Br and 12 O atoms
Isotropic temperature factors	None	For 100 C + 4 N + 22 O atoms

* Sealed in a glass capillary tube.
† Ratio of the number of observed reflections to the number of theoretically possible reflections in the same angular range.
‡ Calculated by Wilson's method.

anomalous-dispersion method gave no more information than that given by the usual heavy-atom method, because of large errors in the intensity measurements caused by the broad and low peak intensities of the reflections. Several cycles of Fourier and difference Fourier syntheses and block-diagonal least-squares calculations revealed the whole structure which was refined to an R of 0·125 (Table 1). The absolute configuration (Fig. 1) was determined by the anomalous-dispersion method using intensities of 200 hkl $h\bar{k}l$ pairs.

An attempt to determine the structure of (II), involving phase-angle determination by the isomorphous-replacement method, including the anomalous-dispersion effect of the iodine derivative (II′), was not successful. This was also due to the poor quality of the intensity data for (II′) and the lack of strict isomorphism between (II) and (II′), because of the disordered arrangement of the Br atoms. The locations of four independent I atoms in (II′) were finally determined by comparing two Patterson maps, one calculated with $|F(hkl)|^2$ as the coefficient and the other with $[|F(hkl)| - |F(h\bar{k}l)|]^2$. The positions of 60 atoms were determined by the usual Fourier methods for (II′). The complete structure determination then proceeded with the intensity data of the Br derivative (II) assuming the same molecular arrangement as obtained for (II′), and the locations of 142 non-hydrogen atoms were found on the Fourier and difference Fourier maps. At the final stage of the analysis, a disorder of the *m*-bromobenzoyl group was noticed, as shown in Figs. 1 and 2 of a previous paper (Furukawa & Iitaka, 1974). The site-occupancy factors for the *a* and *b* sites in molecule *A* were estimated on the electron density map to be 0·66 for *a* and 0·34 for *b* and these values were fixed in the refinement. The refinement of the atomic parameters was carried out by the block-diagonal least-squares method to an R value of 0·113, in which unit weight was assigned to each reflection.

The absolute configuration (Fig. 1) was determined for (II) by the anomalous-dispersion method based on

Table 2. *The atomic parameters of compound* (I) ($\times 10^3$; *for* I $\times 10^4$)

	x	y	z		x	y	z
I(1)	854 (4)	1005 (2)	1118 (6)	C(36)	435 (3)	438 (1)	350 (5)
I(2)	8137 (3)	4017 (2)	4010 (6)	C(37)	402 (3)	466 (1)	430 (6)
C(1)	84 (5)	220 (2)	722 (7)	C(38)	317 (4)	478 (1)	402 (6)
C(2)	24 (5)	191 (1)	696 (7)	C(39)	426 (3)	448 (1)	198 (5)
C(3)	2 (5)	191 (1)	572 (7)	C(40)	596 (4)	461 (2)	334 (10)
C(4)	14 (3)	220 (2)	489 (6)	C(41)	559 (6)	411 (2)	528 (8)
C(5)	−4 (3)	223 (1)	344 (7)	C(42)	561 (5)	401 (2)	292 (7)
C(6)	15 (4)	251 (1)	287 (4)	C(43)	443 (4)	484 (2)	653 (7)
C(7)	54 (4)	283 (1)	325 (6)	C(44)	434 (4)	472 (1)	790 (7)
C(8)	77 (4)	311 (1)	255 (5)	C(45)	258 (4)	497 (2)	518 (6)
C(9)	125 (5)	335 (1)	297 (6)	C(46)	19 (4)	327 (2)	613 (7)
C(10)	133 (5)	365 (2)	202 (10)	C(47)	−46 (6)	297 (2)	624 (12)
C(11)	184 (4)	391 (1)	263 (6)	C(48)	278 (4)	275 (2)	447 (9)
C(12)	217 (4)	394 (2)	373 (6)	C(49)	205 (5)	172 (3)	336 (8)
C(13)	210 (4)	364 (1)	451 (5)	C(50)	420 (5)	232 (4)	142 (14)
C(14)	154 (4)	335 (2)	408 (6)	C(51)	354 (4)	356 (2)	49 (9)
C(15)	145 (4)	303 (2)	507 (6)	C(52)	867 (6)	318 (2)	409 (9)
C(16)	85 (3)	277 (1)	445 (6)	N(1)	−125 (3)	403 (1)	−63 (5)
C(17)	74 (3)	249 (1)	516 (6)	N(2)	531 (3)	429 (1)	374 (4)
C(18)	136 (4)	230 (1)	876 (7)	O(1)	107 (3)	248 (1)	645 (4)
C(19)	178 (4)	262 (2)	878 (7)	O(2)	−26 (3)	167 (1)	536 (4)
C(20)	216 (5)	268 (2)	1009 (9)	O(3)	29 (4)	313 (1)	140 (6)
C(21)	120 (5)	200 (2)	965 (6)	O(4)	254 (3)	360 (1)	566 (5)
C(22)	−59 (4)	192 (1)	288 (6)	O(5)	107 (2)	319 (1)	627 (4)
C(23)	94 (4)	371 (1)	68 (5)	O(6)	228 (2)	293 (1)	550 (5)
C(24)	3 (4)	386 (1)	80 (6)	O(7)	11 (4)	342 (2)	532 (7)
C(25)	−23 (3)	391 (1)	−79 (4)	O(8)	156 (2)	393 (1)	4 (3)
C(26)	47 (5)	415 (1)	−139 (7)	O(9)	25 (3)	415 (1)	−272 (4)
C(27)	131 (3)	395 (1)	−131 (6)	O(10)	36 (4)	472 (1)	−268 (5)
C(28)	−167 (10)	379 (4)	24 (11)	O(11)	266 (2)	446 (1)	360 (4)
C(29)	−165 (4)	402 (2)	−212 (7)	O(12)	406 (2)	461 (1)	575 (3)
C(30)	−134 (4)	436 (1)	−12 (6)	O(13)	474 (2)	508 (1)	619 (4)
C(31)	30 (6)	445 (2)	−329 (6)	O(14)	277 (6)	196 (2)	347 (8)
C(32)	39 (6)	435 (2)	−493 (12)	O(15)	374 (5)	193 (2)	144 (5)
C(33)	212 (5)	418 (2)	−212 (9)	O(16)	435 (3)	355 (1)	81 (6)
C(34)	291 (3)	414 (1)	423 (8)	O(17)	817 (4)	305 (1)	280 (7)
C(35)	377 (3)	406 (1)	383 (8)	O(18)	−171 (8)	488 (2)	−367 (8)

Table 3. *The atomic parameters of compound* (II) ($\times 10^3$ *for* C, N *and* O *and* $\times 10^4$ *for* Br)

For atoms in molecule *B*, 100 is added to the atom numbers, and for benzene atoms, 200 is added. Br(2) and Br(3) are the Br atoms at sites *a* and *b* respectively.

	x	*y*	*z*		*x*	*y*	*z*
Br(1)	2596 (4)	1519 (2)	−1115 (5)	C(47)	−77 (2)	268 (1)	154 (3)
Br(2)	−3113 (5)	2631 (4)	3390 (11)	C(101)	470 (2)	567 (1)	34 (3)
Br(3)	−2756 (8)	2001 (3)	82 (14)	C(102)	433 (2)	534 (1)	43 (2)
Br(101)	−2185 (5)	5468 (2)	3636 (6)	C(103)	450 (2)	506 (1)	52 (3)
Br(102)	−4315 (3)	3821 (1)	−214 (4)	C(104)	534 (3)	497 (1)	51 (4)
C(48)	−147 (2)	257 (1)	155 (3)	C(105)	408 (2)	475 (1)	51 (2)
C(49)	−185 (2)	265 (1)	232 (4)	C(106)	422 (2)	446 (1)	63 (2)
C(50)	−263 (3)	251 (1)	231 (4)	C(107)	374 (2)	423 (1)	65 (3)
C(51)	−280 (3)	229 (1)	158 (3)	C(108)	292 (1)	434 (1)	55 (2)
C(52)	−237 (3)	221 (1)	87 (3)	C(109)	243 (2)	411 (1)	48 (2)
C(53)	−171 (2)	235 (1)	79 (3)	C(110)	250 (2)	375 (1)	38 (2)
C(133)	−212 (2)	632 (1)	227 (3)	C(111)	172 (2)	425 (1)	42 (2)
C(134)	−283 (2)	645 (1)	246 (3)	C(112)	160 (2)	457 (1)	42 (2)
C(135)	−321 (3)	621 (1)	283 (4)	C(113)	86 (2)	467 (1)	47 (3)
C(136)	−318 (3)	597 (1)	326 (5)	C(114)	70 (2)	501 (1)	48 (2)
C(137)	−249 (3)	588 (1)	328 (4)	C(115)	8 (2)	515 (1)	59 (2)
C(138)	−187 (2)	604 (1)	265 (3)	C(116)	−6 (1)	550 (1)	54 (2)
C(1)	545 (2)	511 (1)	318 (3)	C(117)	46 (2)	569 (1)	49 (2)
C(2)	460 (2)	513 (1)	304 (3)	C(118)	119 (2)	557 (1)	40 (2)
C(3)	425 (2)	540 (1)	296 (2)	C(119)	130 (1)	524 (1)	47 (2)
C(4)	454 (2)	575 (1)	302 (3)	C(120)	200 (2)	513 (1)	42 (3)
C(5)	351 (2)	536 (1)	295 (3)	C(121)	212 (2)	479 (1)	45 (2)
C(6)	306 (2)	563 (1)	296 (2)	C(122)	283 (2)	466 (1)	48 (2)
C(7)	230 (2)	559 (1)	290 (3)	C(123)	37 (2)	608 (1)	50 (2)
C(8)	203 (2)	524 (1)	298 (2)	C(124)	43 (2)	618 (1)	157 (2)
C(9)	137 (1)	513 (1)	303 (2)	C(125)	22 (2)	654 (1)	169 (2)
C(10)	76 (2)	538 (1)	298 (3)	C(126)	−42 (2)	658 (1)	112 (3)
C(11)	120 (2)	482 (1)	302 (3)	C(127)	−44 (2)	645 (1)	15 (2)
C(12)	168 (1)	459 (1)	301 (2)	C(128)	−114 (2)	650 (1)	−31 (3)
C(13)	140 (2)	425 (1)	299 (2)	C(129)	74 (2)	676 (1)	124 (3)
C(14)	197 (2)	396 (1)	305 (2)	C(130)	73 (2)	651 (1)	333 (3)
C(15)	174 (1)	364 (1)	304 (2)	C(131)	−11 (2)	691 (1)	302 (3)
C(16)	225 (2)	341 (1)	312 (2)	C(132)	−163 (2)	657 (1)	191 (3)
C(17)	290 (2)	349 (1)	327 (2)	C(139)	−61 (2)	492 (1)	68 (2)
C(18)	315 (1)	382 (1)	320 (2)	C(140)	−61 (2)	479 (1)	171 (2)
C(19)	267 (1)	405 (1)	307 (2)	C(141)	−127 (2)	456 (1)	178 (2)
C(20)	289 (2)	439 (1)	303 (2)	C(142)	−188 (2)	481 (1)	161 (2)
C(21)	236 (2)	465 (1)	299 (2)	C(143)	−183 (2)	496 (1)	63 (3)
C(22)	259 (2)	499 (1)	301 (2)	C(144)	−238 (2)	522 (1)	44 (3)
C(23)	351 (2)	323 (1)	335 (2)	C(145)	−100 (2)	406 (1)	272 (3)
C(24)	383 (2)	317 (1)	236 (2)	C(146)	−122 (2)	457 (1)	357 (3)
C(25)	441 (2)	289 (1)	245 (2)	C(147)	−300 (2)	457 (1)	224 (2)
C(26)	400 (2)	260 (1)	294 (3)	C(148)	−351 (2)	431 (1)	206 (2)
C(27)	363 (2)	268 (1)	391 (3)	C(149)	−397 (2)	424 (1)	281 (3)
C(28)	326 (2)	242 (1)	440 (3)	C(150)	−451 (2)	403 (1)	266 (2)
C(29)	496 (2)	299 (1)	305 (2)	C(151)	−461 (2)	392 (1)	183 (3)
C(30)	472 (2)	305 (1)	74 (2)	C(152)	−425 (2)	396 (1)	111 (3)
C(31)	515 (2)	254 (1)	138 (3)	C(153)	−359 (2)	420 (1)	121 (2)
C(32)	358 (2)	221 (1)	184 (3)	C(201)	640 (3)	158 (1)	422 (4)
C(33)	293 (2)	215 (1)	118 (2)	C(202)	579 (3)	162 (2)	388 (5)
C(34)	231 (2)	228 (1)	128 (3)	C(203)	586 (3)	164 (1)	280 (4)
C(35)	173 (2)	222 (1)	60 (3)	C(204)	636 (3)	154 (1)	231 (4)
C(36)	189 (2)	198 (1)	−6 (3)	C(205)	701 (3)	147 (1)	294 (4)
C(37)	244 (2)	182 (1)	−11 (3)	C(206)	714 (3)	142 (1)	387 (5)
C(38)	300 (2)	192 (1)	47 (3)	O(1)	324 (1)	505 (0)	299 (1)
C(39)	100 (2)	354 (1)	291 (2)	O(2)	188 (1)	580 (1)	292 (2)
C(40)	81 (2)	353 (1)	189 (2)	O(3)	82 (1)	418 (0)	283 (2)
C(41)	10 (2)	336 (1)	168 (2)	O(4)	385 (1)	388 (0)	326 (1)
C(42)	13 (2)	306 (1)	215 (2)	O(5)	351 (1)	446 (1)	305 (2)
C(43)	31 (2)	307 (1)	316 (2)	O(6)	322 (1)	295 (1)	374 (2)
C(44)	36 (2)	277 (1)	373 (3)	O(7)	348 (1)	248 (0)	232 (2)
C(45)	37 (2)	321 (1)	0 (3)	O(8)	403 (1)	203 (1)	195 (2)
C(46)	−40 (2)	367 (1)	36 (3)	O(9)	97 (1)	321 (0)	328 (2)

Table 3 (*cont.*)

	x	*y*	*z*		*x*	*y*	*z*
O(10)	−61 (1)	292 (0)	213 (2)	O(108)	−172 (1)	685 (1)	165 (2)
O(11)	−36 (1)	260 (1)	93 (2)	O(109)	−115 (1)	514 (0)	61 (2)
O(101)	338 (1)	486 (0)	54 (1)	O(110)	−250 (1)	459 (1)	152 (2)
O(102)	382 (1)	394 (1)	75 (2)	O(111)	−290 (1)	473 (1)	295 (2)
O(103)	43 (1)	448 (1)	44 (2)	N(1)	459 (1)	280 (1)	144 (2)
O(104)	169 (1)	580 (0)	36 (2)	N(2)	−4 (1)	335 (1)	60 (2)
O(105)	247 (1)	534 (0)	38 (2)	N(101)	14 (1)	658 (1)	273 (2)
O(106)	−31 (1)	612 (0)	13 (2)	N(102)	−135 (1)	439 (1)	268 (2)
O(107)	−99 (1)	640 (1)	169 (2)				

543 Friedel pairs. The atomic parameters of (I) and (II) are listed in Tables 2 and 3.*

Description and discussion of the structures

The structure of (I)

A stereoscopic drawing of (I) is given in Fig. 1(*b*) of a previous paper (Furukawa, Itai & Iitaka, 1973). The bond lengths are summarized in Table 4 which can be compared with those found in (II) (Table 5).

It is now established that the skeleton of kidamycin is a tetracyclic anthraceno[1,2-*b*]pyran system consisting of four fused rings, *A*, *B*, *C*, *D*, and two tetrahydropyran rings, *E* and *F*, which are attached to ring *D* through C-glycosidic linkages. The conformations of the *E* and *F* rings will be discussed later and compared with those found in (II).

The methoxy group in ring *C* is undoubtedly added by the methanolysis reaction of triacetylkidamycin bis(trimethylammonium) iodide with the solvent.

The structure of (II)

A stereoscopic drawing of (II) is given in Fig. 2 of a previous paper (Furukawa & Iitaka, 1974). The bond lengths found in the two crystallographically independent molecules, *A* and *B*, are summarized in Table 5.

The outstanding feature of the crystal structure of (II) is the stacking of the chromophores. As can be seen in Fig. 2 of Furukawa & Iitaka (1974), molecules *A* and *B* are related by a pseudo-diad axis roughly parallel to the anthraquinone ring and running halfway between the *A* and *B* molecules. These pairs of molecules are related by a [001] crystallographic screw diad axis. The molecules are therefore arranged radially around the screw diad axis with their chromophore planes parallel to each other with an average interplanar distance of $c/4 = 3{\cdot}48$ Å. In the crystal structure of (I), no such stacking of the chromophores was observed because the planarity of ring *C* was destroyed by the methanolysis reaction.

Comparison of the structures of (I) *and* (II)

The torsion angles representing the orientation of the pyran ring and other substituent groups with respect to the chromophore are listed in Table 6.

Although the accuracy of the present determination is not high, the bond lengths and angles are compatible with the chemical structure and in agreement with those reported for anthraquinone (Blockmann, 1968) and pyran (Blufani & Keller-Schierlein, 1966; Johnson, Smith & Guthrie, 1972).

At first sight, the structures of (I) and (II) seem to be very similar. However, an essential difference suggesting the mechanism of the isomerization reaction

* Lists of structure factors, thermal parameters and bond angles for compounds (I) and (II) have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 34941 (29 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. The atom numbering adopted here is, with the exception of Tables 2 and 3, identical with that given in the previous paper (Furukawa *et al.*, 1975).

Table 4. *Bond lengths* (Å) *of compound* (I)

Bond type	Number of bonds	Average value Length	E.s.d.	Av.*	Max.†	Min.‡
Chromophore						
Endocyclic						
C–C	2	1·57	0·08	0·025	1·62	1·52
C⋯C	17	1·393	0·086	0·046	1·52	1·22
C–O in C–O–C	2	1·41	0·08	–	1·41	1·41
Exocyclic						
C–C	7	1·574	0·097	0·041	1·81	1·49
C=C	1	1·41	0·08	–	–	–
C–O in C–O–C	5	1·432	0·076	0·021	1·49	1·36
C=O	3	1·16	0·09	0·070	1·38	1·01
Tetrahydropyran ring						
Endocyclic						
C–C	8	1·531	0·075	0·031	1·67	1·43
C–O in C–O–C	4	1·48	0·065	0·021	1·56	1·43
Exocyclic						
C–C	5	1·634	0·098	0·043	1·76	1·47
C=O	2	1·19	0·085	0·023	1·23	1·14
C–O in C–O–C	4	1·39	0·075	0·028	1·48	1·32
C–N	8	1·580	0·089	0·054	1·78	1·41

* Av.: average value of differences.
† Max.: the maximum value of the bond lengths.
‡ Min.: the minimum value of the bond lengths.

Table 5. *Bond lengths* (Å) *of compound* (II)

Bond type	Number of bonds	Average value Molecule *A*	Molecule *B*	*A*,*B*av.*	Av.†	Max.‡	Min.§
Chromophore							
Endocyclic							
C⋯C	38	1·42 (4)	1·4 (4)	1·417	0·037	1·62	1·22
C–O in C–O–C	4	1·33 (4)	1·40 (4)	1·365	0·03	1·44	1·28
Exocyclic							
C–C	12	1·56 (4)	1·58 (5)	1·567	0·027	1·65	1·42
C=C	2	1·29 (5)	1·21 (5)	1·25	0·03	1·29	1·21
C–O	2	1·38 (3)	1·35 (4)	1·37	0·01	1·38	1·35
C=O	6	1·21 (4)	1·20 (4)	1·206	0·018	1·26	1·14
Tetrahydropyran ring							
Endocyclic							
C–C	16	1·52 (5)	1·53 (5)	1·526	0·023	1·60	1·43
C–O in C–O–C	8	1·41 (4)	1·42 (4)	1·417	0·015	1·49	1·37
Exocyclic							
C–O	10	1·46 (5)	1·50 (5)	1·483	0·013	1·56	1·42
C–O in C–O–C	8	1·40 (4)	1·48 (4)	1·435	0·030	1·54	1·31
C=O	4	1·19 (5)	1·20 (4)	1·19	0·01	1·22	1·15
C–N	12	1·47 (4)	1·47 (4)	1·473	0·022	1·54	1·29
Bromobenzene							
Endocyclic							
C⋯C	24	1·4 (6)	1·38 (6)	1·387	0·045	1·64	1·17

* *A*,*B*av.: average value for molecules *A* and *B*.
† Av.: average value of differences between molecules *A* and *B* and *A*,*B*av.
‡ Max.: the maximum value of the bond lengths in molecules *A* and *B*.
§ Min.: the minimum value of the bond lengths in molecules *A* and *B*.

Table 6. *Torsion angles* (°) *representing the orientation of the pyran rings and other substituent groups with respect to the chromophore*

	Compound (I)	Compound (II) Molecule *A*	Molecule *B*
C(15)–C(14)–C(2)–O(1)	3	3	10
C(9)–C(10)–O(6″)–O(1″)	47	31	26
C(9)–C(8)–C(6′)–O(1′)	32	22	5

from kidamycin to isokidamycin is found at ring *F*. As can be seen in Figs. 1 and 2, the conformations of the pyran rings, *E* and *F* in (I) and (II), are in the chair form except for ring *F* in (I). This conformational difference comes from the difference in the configurations of the asymmetric C atoms of the pyran rings in these compounds. The boat conformation of ring *F* in (I) is a consequence of the repulsions between bulky substituent groups at the 2″, 4″ and 6″ positions. Thus, if it were to take the chair form, the 4″-trimethylamino group would occupy the 1,3-diaxial position with respect to either the 2″-methyl group or ring *D* at the 6″ position.

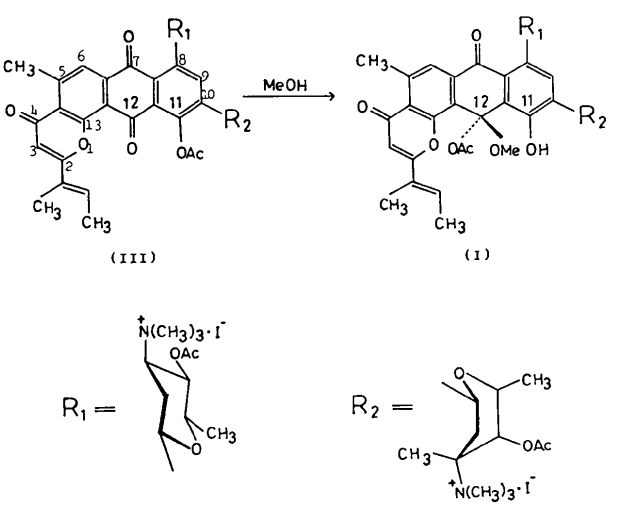

Fig. 2. The migration of the acetyl group from the C(11) to the C(12) position.

In compound (II), the configuration of the 6″ C atom is reversed and no such repulsion arises when the chair conformation is adopted.

The inversion of the chirality of the 6″ C atom is explained by the recyclization of ring *F* during the

isomerization reaction (Furukawa & Iitaka, 1974). The other point of difference in the structures of (I) and (II) is found at ring *C*. As can be seen in Fig. 2, the presence of the geminal methoxy and acetoxy groups at C(12), which lie at the *peri* position with respect to the hydroxyl group at C(11), indicates that the methanolysis reaction of triacetylkidamycin bis(trimethylammonium) iodide (III) [in which one of the acetoxy groups was at C(11)] takes place at C(12) by methoxylation; thereby the migration of the acetyl group from C(11) to C(12) is accomplished.

Comparison of the structures of (I) and (II), along with much chemical and spectroscopic evidence, has led to the structure of kidamycin as shown in Fig. 1, which constitutes a new class of polycyclic microbial metabolites.

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Structural Chemistry of Layered Cyclophanes. VI. Molecular Structures of Triple-Layered [2.2]Paracyclophane Containing Furan and Thiophene Rings

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Abstract

The molecular structures of [2.2](2,5)furano(4,7)[2.2]-paracyclophane and 12,15-dimethyl[2.2](2,5)thiopheno(4,7)[2.2]paracyclophane have been determined by means of X-ray diffraction. The former is monoclinic, with $a = 28{\cdot}066\,(2)$, $b = 16{\cdot}018\,(1)$, $c = 26{\cdot}753\,(2)$ Å, $\beta = 116{\cdot}43\,(1)°$, space group $C2/c$, and $Z = 24$; the latter is also monoclinic, with $a = 15{\cdot}126\,(1)$, $b = 10{\cdot}342\,(1)$, $c = 13{\cdot}321\,(1)$ Å, $\beta = 101{\cdot}87\,(1)°$, space group $P2_1/c$, and $Z = 4$. Both structures were solved by the direct method, and refined anisotropically by the least-squares procedure; $R = 0{\cdot}055$ for non-zero reflexions for the former and 0·066 for the latter. In both molecules, the furan or thiophene ring has an envelope shape, the outer benzene ring is boat-shaped, and the inner benzene ring is twisted by two upper and two lower methylene bridges.

Introduction

Misumi and co-workers synthesized [2.2]paracyclophanes containing (2,5)-bridged five-membered heterocycles. By means of NMR studies at elevated temperature they found inversion of the furan ring but not of the thiophene ring, and they determined energy barriers for the furan-ring inversion. As part of a series of structural studies on layered cyclophanes and in order to obtain information on the ring inversion and the molecular structure, the X-ray structure determination of double- and triple-layered [2.2]paracyclophanes containing five-membered heterocycles has been carried out. This paper deals with the molecular structures of triple-layered [2.2]paracyclophanes containing furan and thiophene rings.

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