DIKETOPIPERAZINES FROM OPTICALLY ACTIVE THIAZOLIDINE-4-CARBOXYLIC ACIDS

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We have previously obtained optically active thiazolidine-4-carboxylic acids by condensing mercapto-amino acids with aldose peracetates [1-4]. In the present communication we shall describe a convenient method for converting these compounds into diketopiperazines.

Although many natural diketopiperazines have already been synthesized [5], the conversion of optically active thiazolidine-4-carboxylic acids (I) to diketopiperazines is unknown in the literature. Several optically inactive diketopiperazines have been obtained from DL-penicillamine in investigations of the structure of penicillin [6] from DL-2-methoxycarbonyl-5,5-dimethylthiazolidine-4-carboxylic acid in pyridine in the presence of tosyl chloride or dicyclohexylcarbodiimide [8, 9].

We have succeeded in obtaining 22 different diketopiperazines with good yields from optically pure acids of type I by cyclodehydration with mesyl chloride in pyridine. Symmetric 1H, 3H, 6H, 8H-bisthiazolo [3,4-a; 3',4'-d]pyrazine-5,-10-diones (II) (diketopiperazines) form rapidly even under mild conditions (from −5 to 0°C). The compounds obtained are high-melting and dissolve poorly in organic solvents. From the data in Table 1 it is seen that this reaction is not accompanied by epimerization, since two individual compounds of type II were obtained from each pair of $C_{(2)}$ epimers of thiazolidine-4-carboxylic acids (Ik and Il, Im and In, Io and Ip). Compounds Io and Iq are enantiomers.

Many reports have been published on the IR spectra of tricyclic diketopiperazines [10, 11]. Bláha [12-14] showed that in compounds with cis annelation the diketopiperazine ring is in the boat conformation, and an absorption band of CO−N at 1420 cm^{-1} is characteristic of such structures. Another characteristic band of this type is observed at 1310 cm^{-1}. In fact, in the case of our tricyclic diketopiperazines of type II, the band of the stretching vibrations of the CO−N bond appears in the 1440-1390-cm^{-1} region, which corresponds to the literature data. The frequency of this band depends on the substituents in the thiazolidine ring: In the case of 1,3,6,8-tetraalkylthiazolidines, it is reduced, and in the case of the polyacetoxyalkyl derivatives, it is increased and appears in the 1440-1420-cm^{-1} region. The amide-I absorption band in the spectra of diketopiperazines IIa-IId is observed in the 1690-1650-cm^{-1} region. In some cases, this band is split. The two carbonyl groups apparently become inequivalent due to the deformation of the diketopiperazine ring. It has been established that in this case, a substitution in the thiazolidine ring influences the frequency of the amide-I band, which, because of the deformation of the ring, is always higher in the 1,3,6,8-tetrasubstituted compounds than in the unsubstituted and 1,6-disubstituted diketopiperazines of type II. The hypothesis that coplanarity of amide group is diminished due to the deformation, i.e., that the frequency of the amide-I band increases, is firmly supported by the spectra of the diketopiperazines with a polyacetoxyalkyl chain, for which this band is observed at a relatively high frequency (1700-1670 cm^{-1}). The amide-I frequencies in the epimeric pairs of diketopiperazines (IIk and IIl, IIm and IIn, IIo, and IIp) differ only slightly from one another, the higher frequency being observed in the compounds which were obtained from the 2,4-cis compounds of type I.

The bands in the 1150-1130 region (of average intensity) and in the 580-550 cm^{-1} region, which are probably caused by skeletal and deformation vibrations of the amide group, are also characteristic. A weak band is observed at 360 cm^{-1} in all cases.

The most probable conformation of the compounds of type II is represented in the following diagram:

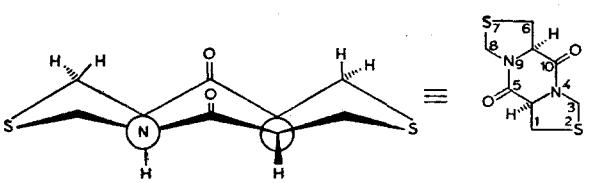

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TABLE 1. Properties of Compounds Synthesized

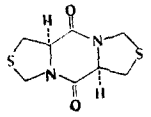
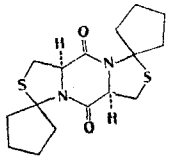
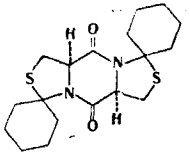
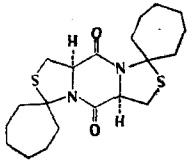
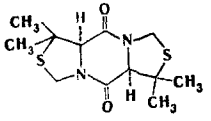
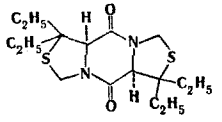
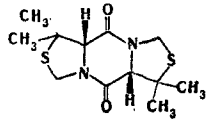
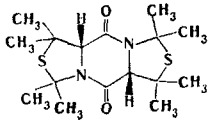
	Compound II	mp, °C (solvent for crystallization)	Found, %				Empirical formula	Calc., %				Yield, %	$[\alpha]_D$, c, t, solvent
			C	H	N	S		C	H	N	S		
a		290 —	—	—	12,1	26,9	$C_8H_{10}N_2O_2S_2$	—	—	12,2	27,8	92	—
b		210—214 (ethanol—water)	56,6	6,6	—	18,7	$C_{16}H_{22}N_2O_2S_2$	56,8	6,6	—	18,9	90	−27, 0,97, 24, DMSO
c		311 (DMFA)	—	—	8,1	17,5	$C_{18}H_{26}N_2O_2S_2$	—	—	7,7	17,6	94	—
d		256—257 —	—	—	6,9	16,7	$C_{20}H_{30}N_2O_2S_2$	—	—	7,1	16,2	61	—
e		210—213 (DMFA – water)	—	—	9,7	22,4	$C_{12}H_{18}N_2S_2O_2$	—	—	9,8	22,4	90	—
f		112—114 (ethanol—water)	52,4	8,2	8,6	20,0	$C_{14}H_{26}N_2O_2S_2$	52,8	8,2	8,8	20,1	77	−101, 0,82, 24, DMSO
g		210—213 (DMFA – water)	—	—	9,6	22,5	$C_{12}H_{18}N_2O_2S_2$	—	—	9,8	22,4	81	—
h		167—168 (ethanol)	—	—	8,1	18,6	$C_{18}H_{26}N_2O_2S_2$	—	—	8,2	18,7	90	+316, 1,00, 22, dioxane

TABLE 1 (continued)

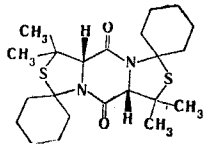
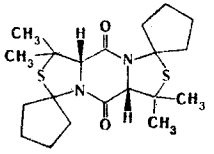
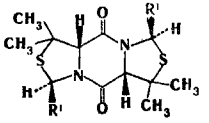
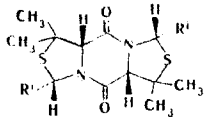
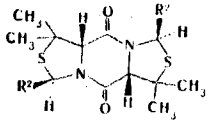
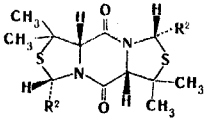
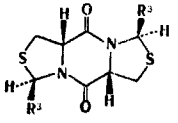
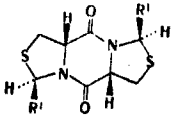
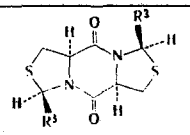
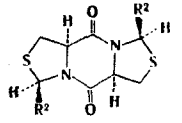
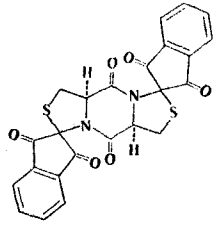
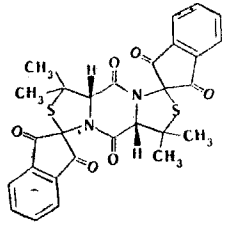
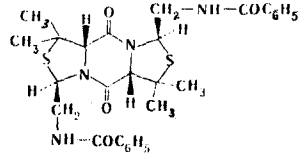
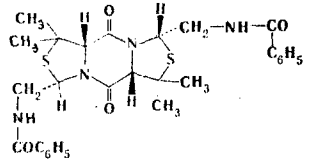
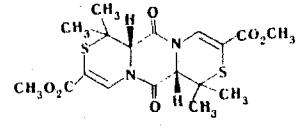
	Compound II	mp, °C (solvent for crystallization)	Found, %				Empirical formula	Calc., %				Yield, %	$[\alpha]_D$, c, l, solvent
			C	H	N	S		C	H	N	S		
i		260 (ethanol)	60,1	6,6	6,9	15,3	$C_{30}H_{34}N_2O_2S_2$	60,2	6,7	7,0	16,7	54	—
j		208—210 (ethanol–water)	60,4	7,5	7,0	16,3	$C_{20}H_{30}N_2O_2S_2$	60,9	7,7	7,1	16,2	30	—
k		Amorphous —	50,3	5,7	—	6,7	$C_{36}H_{50}N_2O_{18}S_2$	50,1	5,8	3,2	7,4	61	+24,5, 0,71, 22, $CHCl_3$
l		236 (ethyl acetate)	50,1	5,9	3,2	7,3	$C_{36}H_{50}N_2O_{18}S_2$	50,1	5,8	3,2	7,4	83	−62 0,97, 24, $CHCl_3$
m		Amorphous —	49,4	6,0	3,4	6,2	$C_{42}H_{58}N_2O_{32}S_2$	50,0	5,8	2,8	6,4	63	+90 1, 23, $CHCl_3$
n		213—215 (ethanol)	49,8	5,7	2,6	6,4	$C_{42}H_{58}N_2O_{32}S_2$	50,0	5,8	2,8	6,4	74	−40 1, 23, $CHCl_3$
o		132—133 (ethanol–water)	47,4	5,1	3,8	7,7	$C_{32}H_{42}N_2O_{18}S_2$	47,6	5,2	3,5	7,9	85	−20 1, 22, $CHCl_3$
p		Amorphous —	47,2	5,1	3,6	7,5	$C_{32}H_{42}N_2O_{18}S_2$	47,6	5,2	3,5	7,9	57	+10 0,81, 21, $CHCl_3$

TABLE 1 (continued)

	Compound II	mp, °C (solvent for crystallization)	Found, %				Empirical formula	Calc., %				Yield, %	$[\alpha]_D$, c, t, solvent
			C	H	N	S		C	H	N	S		
q		130—131 (ethanol–water)	47,4	5,1	3,4	7,9	$C_{32}H_{42}N_2O_{18}S_2$	47,6	5,2	3,5	7,9	90	+21 1, 22, $CHCl_3$
r		Amorphous —	48,0	5,6	3,0	6,7	$C_{38}H_{50}N_2O_{22}S_2$	46,0	5,3	2,9	6,7	75	+54 2,1, 22, $CHCl_3$
s		338—340 (DMFA–water)	—	—	5,7	12,9	$C_{21}H_{14}N_2O_6S_2$	—	—	5,7	13,1	90	−132 0,51, 22, DMSO
t		>360 (DMFA–water)	62,0	4,0	5,5		$C_{28}H_{22}N_2O_6S_2$	61,5	4,1	5,1	11,7	95	+28 1,12, 21, DMFA
u		Amorphous —	62,0	6,3	—	—	$C_{36}H_{36}N_4O_4S_2$	62,0	6,2	—	—	89	+149 0,83, 23, MeOH
v		Amorphous —	62,0	6,4	—	—	$C_{30}H_{36}N_4O_4S_2$	62,0	6,2	—	—	83	+45 1,32, 22, MeOH
w		264—266 (DMFA–water)	49,9	5,4	—	—	$C_{18}H_{22}N_2O_6S_2$	50,7	5,2	—	—	33	—

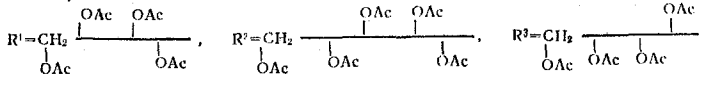
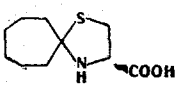
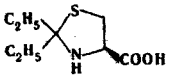
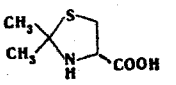
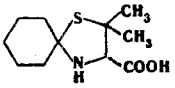
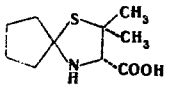


TABLE 2. Infrared Spectra of Diketopiperazines of Type II

Compound II	Amide-I, cm^{-1}	ν_{CO-N}, cm^{-1}	Other characteristic frequencies, cm^{-1}
a	1662	1408	1300, 1155, 530, 355
b	1658	1401	1302, 1148, 562, 550, 355
c	1669 1653	1400	1310, 1128, 570, 560, 360
d	1657	1411	1307, 1150, 560, 555, 350
e	1678 1660	1398	1309, 1122, 531, 517, 349
f	1669 1660	1395	1296, 1154, 573, 563, 360
g	1658	1396	1306, 1296, 1121, 528, 577, 366
h	1670 1660	1396	1302, 1292, 1138, 538, 338
i	1673	1394	1294, 1290, 1134, 578, 560, 370
j	1672	1397	1299, 1289, 1150, 572, 560, 348
k	1677	1425	
l	1681	1415	1290
m	1682	1430	
n	1688	1436	1290, 380
o	1679	1418	1294, 376
p	1684	1432	1292
q	1678	1421	1300, 375
r	1700	1435	350
s	1675	1403	1296, 1160, 548, 530, 340
t	1668	1410	1310, 1294, 1140, 558, 530, 348
u	1667	1422	1310, 1290, 1150, 530, 510, 370
v	1670	1381	1290, 1147, 540, 510, 360
w	1688	1393	1292, 1130, 520, 360

TABLE 3. Thiazolidine-4-carboxylic Acids

Compound I	mp, °C (solvent for crystallization)	Found, % N	Found, % S	Empirical formula	Calc., % N	Calc., % S	Yield, %
 d	Amorphous —	—	12,6	$C_{10}H_{18}ClNO_2S$	5,6	12,7	70
 f	119—120 (diethyl ketone)	7,3	16,7	$C_8H_{15}NO_2S$	7,4	16,9	46,5
 g	127 (acetone)	19,9	8,9	$C_6H_{11}NO_2S$	8,7	19,9	77
 i	176—179 (ethyl acetate–ligroin)	6,2	13,5	$C_{11}H_{21}NO_2S$	6,0	13,9	96
 j	117 (cyclopentanone)	6,3	14,4	$C_{10}H_{17}NO_2S$	6,4	14,8	35

EXPERIMENTAL

The IR spectra were recorded in KBr tablets on a Perkin-Elmer 283 instrument with an accuracy of ±0.5 cm^{-1}. The rotation angles were measured on a Schmidt–Haensch polarimeter. The melting points were determined on a Boëtius micro hot-stage apparatus. The thin-layer chromatography was carried out on Kiesel Gel G, and the preparative separation was carried out in a column with Kiesel Gel 60 in a 4:1 benzene–acetone system with detection by iodine vapor.

The starting compounds used were commercial L-cysteine (from Reanal), D-cysteine (from Diamalt AG, West Germany), and D-penicillamine (from Biogal, Hungary).

The thiazolidine-4-carboxylic acids were obtained according to the following methods: Ia [15]), Ib [16], Ic [17], Ie [18]) Ih [19], Ik and Il [20], Im and In [4], Io and Ip [2], Iq and Ir [3], Is and It [21], Iu and Iv [22], and

Iw [23]. The synthesis of the acids that have not been described was carried out in analogy to the methods for the compounds described: Id [17], If and Ig [18], and Ii and Ij [17] (Table 3).

Diketopiperazines IIa-IIw

A solution of 1 mmole of compound I in 5 ml of dry pyridine is cooled to −10°C, and 0.11 ml of methanesulfonyl chloride is added with stirring. The stirring is continued at room temperature for another 2 h. The homogeneous mass is poured into 40 ml of water, and the amorphous oily precipitate formed is extracted with chloroform. The extract is washed with a $KHSO_4$ solution and dried with $MgSO_4$. The further purification is carried out in a chromatographic column or by crystallization. The data on the diketopiperazines obtained are presented in Table 1.

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