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REACTION OF 5,5-DIPHENYL-2-THIOHYDANTOIN WITH 1,3-DIBROMOPROPANE UNDER PHASE TRANSFER CATALYTIC CONDITIONS

CRYSTAL AND MOLECULAR STRUCTURE OF 2,3,4,5-TETRAHYDRO-7,7-DIPHENYLIMIDAZO-[2,1-b]-THIAZINE-6(7H)-ONE

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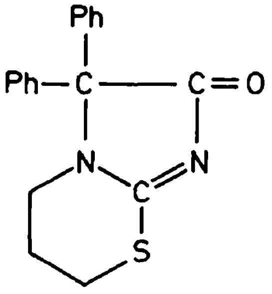
Abstract The reaction of the potassium salt of 5,5-diphenyl-2-thiohydantoin with 1,3-dibromopropane and triethylamine carried out under phase transfer catalytic conditions gave almost quantitatively two isomeric diphenylimidazothiazine 2 and 3 in a ratio *ca* 1:2. 2,3,4,5-Tetrahydro-7,7-diphenylimidazo-[2,1-b]-thiazine-6(7H)-one (3) crystallises from DMSO in the space group $P2_12_12_1$ with $a = 8.488(3)$, $b = 11.682(4)$, $c = 15.522(5)$ Å. The 6-membered thiazine ring in 3 adopts a sofa conformation.

As part of our program concerning the structure-activity relationship of 5,5-diphenyl-2-thiohydantoin (**1**) derivatives we recently reported[1] the reaction of **1** with 1,3-dibromopropane. It was found to give two isomeric bicyclic products **2** and **3** the yield and ratio of which are strongly dependent on the reaction conditions.

Thus, alkylation of the potassium salt of **1** with 1,3-dibromopropane in anhydrous dimethoxyethane (DME) gave a mixture of **2** and **3** in moderate yields in the respective ratio of 1.8:1. When the reaction of **1** with 1,3-dibromopropane was carried out in EtOH–H_2O solution using an equimolar quantity of sodium hydroxide as a base, compound **3** was the only isolated product since its simultaneously formed isomer **2** was further hydrolysed under these conditions.

We found now that it is very advantageous to alkylate **1** under two phase catalytic conditions.[2] The following experimental procedure was applied. The reaction of the potassium salt of **1** with 1,3-dibromopropane was carried out in a benzene-water mixture at 40–45° for 5 hr in the presence of equimolar amount of triethylamine and a catalytic amount of hexadecyltributylphosphonium bromide as a phase transfer catalyst. The reaction is quantitative under



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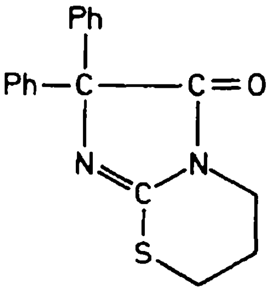

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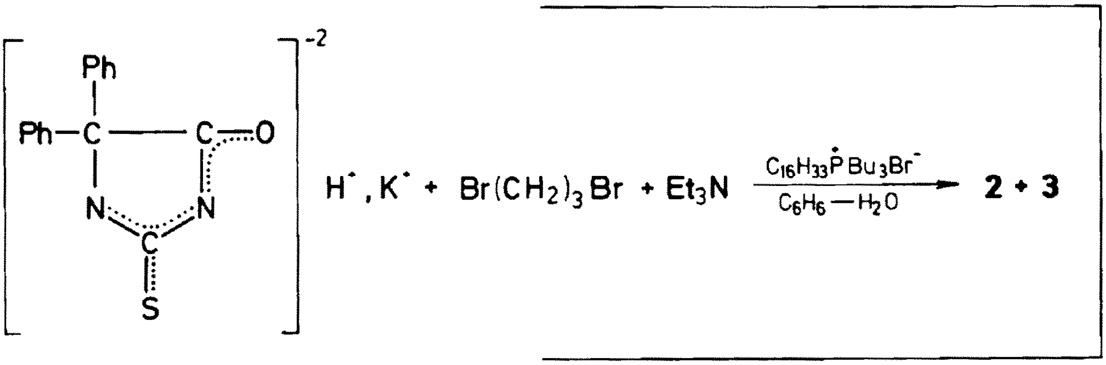
these conditions and resulted in the formation of a mixture of **2** and **3** in a ratio 1 : 2. It is interesting to note that **3** is formed as a major product of the reaction under PTC-conditions.



The facile isolation of **3** prompted us to determine its crystal and molecular structure in order to establish the conformation of the 6-membered thiazine ring in **3** and to make some comparisons between the structural parameters of **2** and **3**.

The solid state conformation of **3** with the appropriate molecular atom numbering is shown in Fig. 1. The packing of the molecules of **3** in the unit cell is shown in Fig. 2. Fractional atomic coordinates and thermal parameters are listed in Tables 1 and 2. Interatomic distances and valency and torsion angles are given in Tables 3 and 4. The molecule of **3** may be described in terms of three planes: two planes of the benzene rings and the plane of the condensed hydantoin and thiazine rings. Both benzene rings as well as hydantoin ring are planar within experimental error. These planes are given in Table 5 (plane 1, 2 and 3). The dihedral angles between the best plane of the hydantoin ring and the benzene rings are 62.8° and 129.8°, respectively.

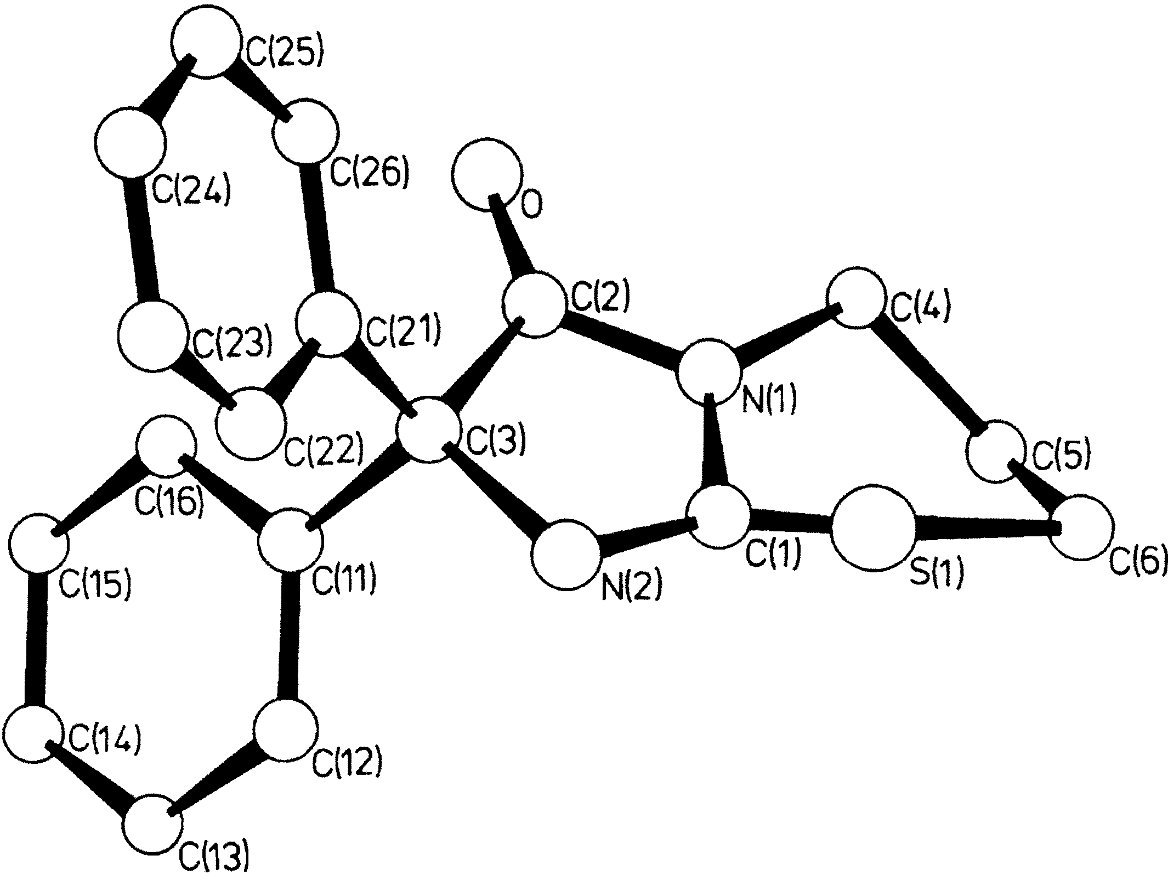


Fig. 1 Perspective view of the molecule of 3 with the numbering scheme.

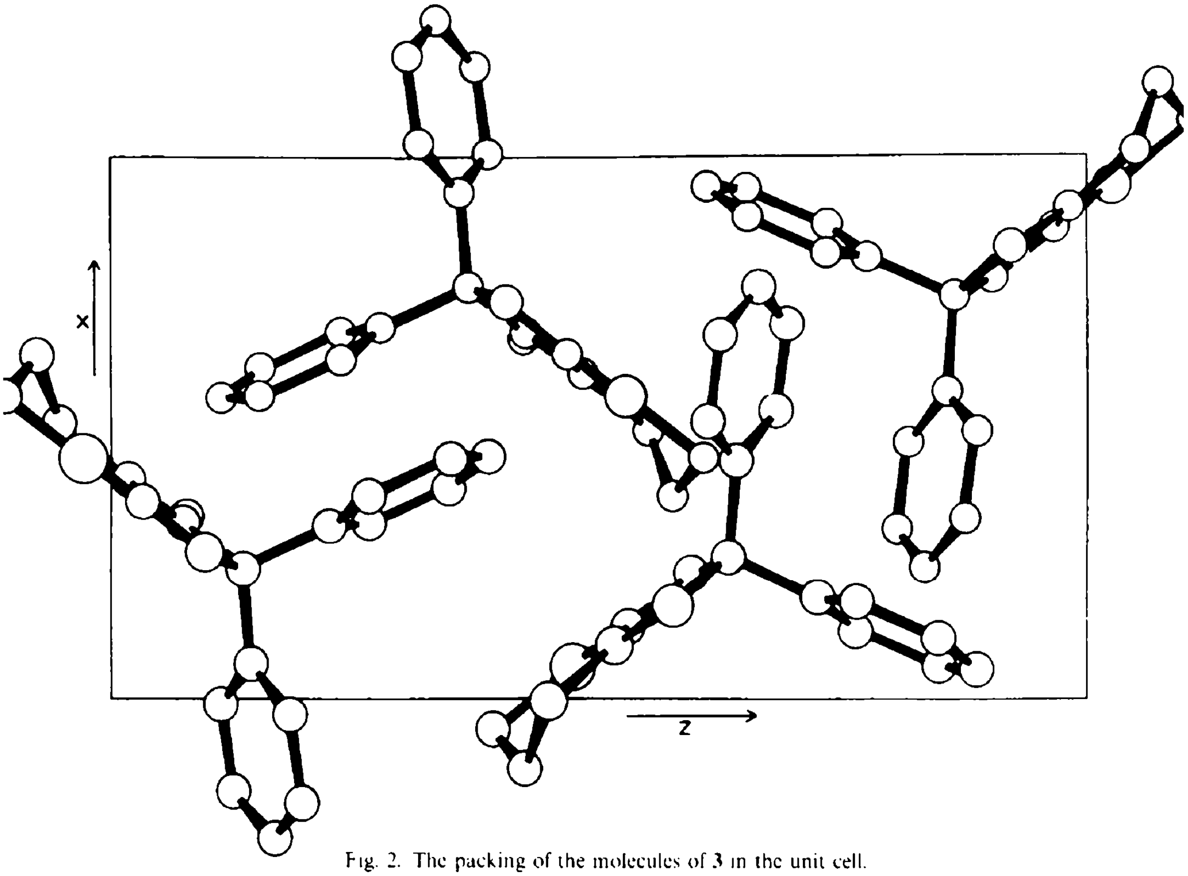


Fig. 2. The packing of the molecules of 3 in the unit cell.

Table 1. Fractional atomic coordinates (× 10^4) for non-hydrogen atoms with estimated standard deviations in parentheses

Atom	x	y	z
S	578(1)	-2109(1)	4722(1)
O	1698(3)	1865(2)	5756(2)
N(1)	967(3)	158(2)	5158(2)
N(2)	2294(3)	-1150(2)	5950(2)
C(1)	1348(4)	-978(3)	5313(2)
C(2)	1746(4)	831(3)	5748(2)
C(3)	2595(4)	-10(3)	6339(2)
C(4)	-70(5)	628(4)	4488(2)
C(5)	-1291(5)	-267(4)	4245(3)
C(6)	-591(5)	-1368(4)	3912(2)
C(11)	1841(4)	55(3)	7241(2)
C(12)	1252(5)	-898(3)	7643(3)
C(13)	601(5)	-787(4)	8476(3)
C(14)	541(5)	256(5)	8867(3)
C(15)	1100(5)	1221(4)	8461(3)
C(16)	1761(5)	1119(4)	7653(3)
C(21)	4378(4)	196(3)	6418(2)
C(22)	5280(5)	-619(3)	6820(3)
C(23)	6892(5)	-450(5)	6937(3)
C(24)	7580(5)	544(5)	6660(3)
C(25)	6705(6)	1347(5)	6251(4)
C(26)	5090(5)	1174(4)	6126(3)

Table 2. Hydrogen atom fractional coordinates and isotropic thermal parameters

Atom	x	y	z	U
H(41)	-43(4)	141(3)	471(2)	61
H(42)	49(4)	75(3)	400(2)	61
H(51)	-186(4)	-41(3)	471(2)	68
H(52)	-207(4)	6(3)	382(2)	68
H(61)	14(4)	-116(3)	339(2)	64
H(62)	-141(4)	-200(3)	368(2)	64
H(121)	129(4)	-160(3)	736(2)	53
H(131)	23(5)	-155(3)	867(2)	69
H(141)	21(4)	27(3)	941(2)	64
H(151)	96(4)	200(3)	877(2)	67
H(161)	231(4)	178(3)	733(2)	56
H(221)	476(4)	-134(3)	710(2)	57
H(231)	754(4)	-101(3)	723(2)	69
H(241)	855(5)	67(3)	674(2)	78
H(251)	726(4)	203(3)	586(2)	91
H(261)	453(5)	171(4)	585(2)	72

Table 3. Interatomic distances (Å) and angles ( ) with estimated standard deviations in parentheses

a. Bond lengths

C(1) -S	1.736(3)	C(6) -S	1.820(4)
C(2) -O	1.209(4)	C(1) -N(1)	1.387(4)
C(2) -N(1)	1.376(4)	C(4) -N(1)	1.469(5)
C(1) -N(2)	1.290(4)	C(3) -N(2)	1.484(4)
C(2) -C(3)	1.526(5)	C(11)-C(3)	1.541(5)
C(21)-C(3)	1.537(5)	C(4) -C(5)	1.521(6)
C(5) -C(6)	1.508(7)	C(11)-C(12)	1.370(5)
C(16)-C(11)	1.399(5)	C(12)-C(13)	1.412(6)
C(14)-C(13)	1.362(7)	C(14)-C(15)	1.376(7)
C(15)-C(16)	1.380(6)	C(21)-C(22)	1.372(5)
C(26)-C(21)	1.370(6)	C(23)-C(22)	1.394(6)
C(24)-C(23)	1.369(8)	C(25)-C(24)	1.355(8)
C(26)-C(25)	1.399(6)		

b. Valency angles

C(6) -S -C(1)	102.0(2)	C(2) -N(1) -C(1)	108.6(3)
C(4) -N(1) -C(1)	128.3(3)	C(4) -N(1) -C(2)	123.1(3)
C(3) -N(1) -C(1)	106.3(3)	N(1) -C(1) -S	123.3(2)
N(2) -C(1) -S	121.4(3)	N(2) -C(1) -N(1)	115.2(3)
N(1) -C(2) -O	124.2(3)	C(3) -C(2) -O	130.8(3)
C(3) -C(2) -N(1)	105.1(3)	C(2) -C(3) -N(2)	104.5(3)
C(11) -C(3) -N(2)	110.0(3)	C(11) -C(3) -C(2)	108.6(3)
C(21) -C(3) -N(2)	110.0(3)	C(21) -C(3) -C(2)	114.4(3)
C(21) -C(3) -C(11)	109.2(3)	C(5) -C(4) -N(1)	109.1(3)
C(6) -C(5) -C(4)	113.8(4)	C(5) -C(6) -S	112.6(3)
C(12)-C(11) -C(3)	121.7(3)	C(16)-C(11) -C(9)	118.6(3)
C(16)-C(11) -C(12)	119.7(3)	C(13)-C(12) -C(11)	119.1(4)
C(14)-C(13) -C(12)	120.3(4)	C(15)-C(14) -C(13)	121.1(4)
C(16)-C(15) -C(14)	119.0(4)	C(15)-C(16) -C(11)	120.8(4)
C(22)-C(21) -C(3)	118.5(3)	C(26)-C(21) -C(3)	122.6(3)
C(26)-C(21) -C(22)	118.9(4)	C(23)-C(22) -C(21)	120.6(4)
C(24)-C(26) -C(22)	119.8(4)	C(25)-C(24) -C(23)	120.1(4)
C(26)-C(25) -C(24)	120.1(5)	C(25)-C(26) -C(21)	120.5(4)

Table 4. Torsion angles ( ) in thiazine ring, σ range 0.5–1.1

C(4)-N(1)-C(1)-S	-1.9
C(1)-N(1)-C(4)-C(5)	27.1
C(6)-S -C(1)-N(1)	3.8
C(1)-S -C(6)-C(5)	-32.6
N(1)-C(4)-C(5)-C(6)	-58.9
C(4)-C(5)-C(6)-S	63.9

The asymmetry parameter :

$$\Delta C_S = \sqrt{\sum_{i=1}^{m} (\phi_i + \phi_i)^2/3} \qquad \Delta C_S^{C(1)} = 4.4^\circ$$

The test of conformation :

$$I = < |\phi_i - \phi_{i+3}| > = 62.7^\circ$$

$$II = \Sigma\, |\phi_i - \phi_{i+1}| = 376.4^\circ$$

$$III = \Sigma\, |\phi_i| = 188.2^\circ$$

$$IV = \Sigma\, |\phi_i - \phi_{i+3}| = 188.2^\circ$$

$$V = \Sigma\, \Big|\, |\phi_i| - |\phi_{i+1}| \,\Big| = 124$$

If I < 95, II = 2 III, III = IV the ring adopts a half-chair or sofa conformation

Table 5 Least-squares planes and displacements (Å) of atoms from these planes (the atoms not used for defining the plane are denoted by asterisks)

1. -1.5802 X + 5.1025 Y + 13.6612 Z - 8.1687
2. 7.6265 X - 1.8911 Y + 6.3342 Z = 5.9761
3. 6.7583 X + 0.9444 Y - 9.3073 Z = -4.1172
4. 6.6824 X + 0.8196 Y - 9.5093 Z = -4.2489

Plane 1		Plane 2	
C(21)	0.007(3)	C(11)	0.005(4)
C(22)	0.001(4)	C(12)	-0.008(4)
C(23)	-0.009(5)	C(13)	0.003(4)
C(24)	0.010(5)	C(14)	0.006(4)
C(25)	-0.002(6)	C(15)	-0.009(4)
C(26)	-0.007(4)	C(16)	0.003(4)
$\chi^2 = 6.5$		$\chi^2 = 13.9$	

Plane 3		Plane 4	
S*	-0.086(1)	S	-0.028(1)
O*	0.085(3)	N(1)	0.003(3)
N(1)	-0.015(3)	C(1)	0.020(3)
N(2)	0.024(3)	C(4)	-0.017(4)
C(1)	-0.006(3)	C(6)	0.022(4)
C(2)	0.027(3)	C(5)*	-0.673(4)
C(3)	-0.030(3)		
C(4)*	-0.050(4)		

Some dihedral angles between planes e.s.d.'s range 0.5-1.1°

$1 \wedge 2 = 83.0^\circ \qquad 1 \wedge 3 = 129.8^\circ \qquad 2 \wedge 3 = 62.8^\circ$

$3 \wedge 4 = 2.6^\circ$

Table 6. Anisotropic thermal parameters[*] (× 10^3) for non-hydrogen atoms with estimated standard deviations in parentheses.

In the form

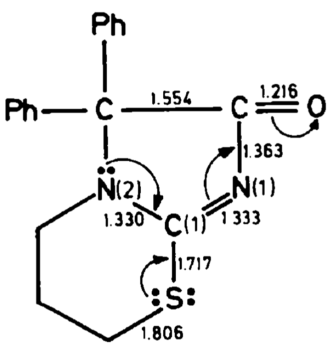
$$B \sin^2 \theta/\lambda^2 = 2\pi^2 (U_{11} h^2 a^{x2} + U_{22} k^2 b^{x2} + U_{33} l^2 c^{x2} + 2 U_{12} hk\, a^x b^x + 2 U_{13} hl\, a^x c^x + 2 U_{23} kl\, b^x c^x)$$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
S	85(1)	55(1)	47(1)	-5(1)	-9(1)	-23(1)
O	72(2)	43(2)	83(2)	-8(1)	-12(2)	8(1)
N(1)	42(2)	45(2)	44(2)	2(1)	-12(1)	-4(1)
N(2)	53(2)	41(2)	40(2)	-5(1)	-4(1)	1(1)
C(1)	44(2)	46(2)	34(2)	3(2)	3(2)	-9(2)
C(2)	41(2)	35(2)	54(2)	3(2)	3(2)	3(2)
C(3)	36(2)	35(2)	42(2)	-6(2)	-4(2)	0(1)
C(4)	54(2)	82(3)	50(2)	10(2)	-19(2)	-4(2)
C(5)	55(3)	101(4)	57(2)	2(3)	-12(2)	-2(3)
C(6)	69(3)	85(3)	48(2)	-1(2)	-12(2)	-28(3)
C(11)	30(2)	43(2)	45(2)	-3(2)	-6(2)	0(2)
C(12)	49(2)	60(2)	56(2)	0(2)	-3(2)	0(2)
C(13)	53(3)	91(3)	62(3)	20(3)	5(2)	-4(3)
C(14)	50(2)	117(4)	48(2)	16(2)	5(2)	8(3)
C(15)	55(3)	93(3)	57(2)	-26(3)	8(2)	-3(3)
C(16)	48(2)	72(3)	56(2)	-16(2)	2(2)	-6(2)
C(21)	37(2)	53(2)	41(2)	-16(2)	-1(2)	5(2)
C(22)	52(3)	56(2)	64(2)	-5(2)	-8(2)	6(2)
C(23)	49(3)	93(4)	76(3)	-18(3)	-12(2)	27(3)
C(24)	35(2)	117(4)	83(3)	-20(3)	-1(2)	-1(3)
C(25)	57(3)	103(4)	120(4)	8(4)	4(3)	-20(3)
C(26)	47(2)	68(3)	94(3)	21(3)	-7(2)	-8(2)

Similarly as in **2**, the 6-membered thiazine ring in **3** was found to be non planar. The torsion angles for this ring are listed in Table 4. Analysis of the torsion angles according to Foces-Foces[3] (Table 4) reveals the sofa conformation for this ring in which the C atom C(5) is 0.673(4) Å off plane. The angle between the plane passing through the atoms S, C(1), N(1), C(4) and C(6) of the thiazine ring and the hydantoin ring is 2.6 . The mirror-plane asymmetry parameter[4] is $\Delta C_s^{C(1)} = 4.4$.

Since **2** and **3** are isomeric compounds differing in the junction of the hydantoin and thiazine rings, it is interesting to point out some differences between their selected interatomic distances (see below).

First of all, the C(1)–N(2) bond in **3** of 1.290(4) Å may be described as a typical double bond in contrast to the C(1)-N(2) bond in **2** which is strongly



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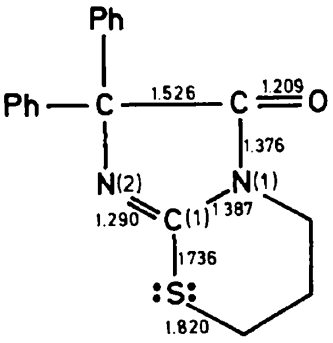

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delocalised. Consequently, the bonds C(1)–N(1) and C(1)–S in **3** are significantly longer than those in **2**. These differences in structural parameters are mainly responsible for a greater chemical reactivity of **3**.

Another difference, which is also a consequence of the different hydantoin–thiazine ring junction, concerns the angle between two benzene rings in **2** and **3**. This angle is 83.0° in the molecule of **3** whereas it is much smaller in **2** and equal to 69.0°.

It should be noted that there are no intermolecular distances shorter than the sum of Van der Waals radii.

EXPERIMENTAL

2,3,4,5-Tetrahydro-6,6-diphenylimidazo-[2,1-b]*-thiazine-7*(6H)*-one* (**2**) *and 2,3,4,5-tetrahydro-7,7-diphenylimidazo-*[2,1-b]*-thiazine-6*(7H)*-one* (**3**)

A soln of 1,3-dibromopropane (1.01 g, 0.005 mol), triethylamine (0.505 g, 0.005 mol) and hexadecyltributylphosphonium bromide (0.126 g, 2.5×10^{-4} mol) in benzene (25 ml) was added to a soln of the K- salt of **1** (1.53 g, 0.005 mol) in water (25 ml). The mixture was stirred at 40–45 for 5 hr. Compound **2** crystallised after cooling from the benzene layer. It was filtered off (0.205 g). The benzene layer was evaporated to dryness and 1.48 g of a white solid was obtained. Tlc analysis (Kiesel gel; benzene: acetone, 20:15) showed 3 spots corresponding to **2**, **3** and the phosphonium catalyst. The isomeric products **2** and **3** were isolated by column chromatography on silica gel (Merck 100–200 mesh). The first fraction separated by elution with benzene-acetone (20:15) was evaporated to dryness to give 0.982 g of the pure **3**, mp 226–227° (63.8%). Elution of a second fraction with EtOH gave **2**, 0.340 g. Recrystallisation of the crude isomer **2** (0.545 g) from n-propanol afforded pure **2** 0.526 g, 34.2%, mp 198–199°. The spectral properties of **2** and **3** obtained as above were identical with those previously reported.

X-Ray structure determination of 3

Crystal data. $C_{18}H_{16}ON_2S$. M = 308.40. Orthorombic, a = 8.488(3), b = 11.682(4), c = 15.522(5) Å, V = 1539 Å^3, Z = 4, F(OOO) = 648, MoK$_\alpha$ radiation, λ = 0.71069 Å, μ MoK$_\alpha$ = 1.70 cm^{-1}; D_m = 1.32 g·cm^{-3}, D_c = 1.338 g·cm^{-3}, space group $P2_12_12_1$ from systematic absences: h00 when h ≠ 2 n, 0k0 when k ≠ 2 n, 00l when l ≠ 2.

Crystallographic measurements. Preliminary data concerning the unit cell dimensions and space group were obtained from oscillation and Weissenberg photographs taken with CuK$_\alpha$ radiation. For intensity measurements on a CAD4 automatic diffractometer a single crystal (crystallised from DMSO) of spherical shape and of diameter *ca* 0.25 mm was used. The intensity data were corrected for the Lorentz and polarisation effects prior to their use in the structural analysis. Absorption corrections were not applied to these data. From a total number of 1508 independent reflections 1368, for which F ⩾ 3.0σ(F) were used for solving and refinement of the structure.

Structure analysis. The structure was solved by direct phase determining methods using TANG program (from SHEL-X-76 system of program on the ODRA 1305 computer) with the 282 reflections with values E ⩾ 1.2. The three origin and two enantiomorph-defining reflections were selected from these reflections. The E-map based on the most self-consistent set of phases allowed the placement of 14 from 22 non-H atoms. A difference Fourier synthesis, phased by this partial structure, provided positions for the remaining 8 non-H atoms. Positional and isotropic thermal parameters were refined by several cycles on full-matrix least-squares calculation to R = 0.133. Further least-squares adjustment of positional and anisotropic thermal parameters of non-H atoms converged at R = 0.077. A difference Fourier synthesis on this stage of refinement showed the positions of all H atoms. The isotropic thermal parameters of H atoms taken as for their parent C atoms were not refined. The process of refinement was stopped when the changes in all parameters became smaller than 1/20 of their respective e.s.d.'s. In the final difference map no significant density was observed. The final R value was 0.045. In the least-squares calculations the weighting scheme $w = k/(\sigma^2 F + gF^2)$ where k = 1.1492 and g = 0.000496 was used.

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