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### SYNTHESIS OF NEW SPIRO HETEROCYCLIC COMPOUNDS DERIVED FROM RHODANINE DERIVATIVES

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# SYNTHESIS OF NEW SPIRO HETEROCYCLIC COMPOUNDS DERIVED FROM RHODANINE DERIVATIVES

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5,5-Dibromo-3-phenyl-2-thioxo-4-thiazolidinone **2**, was reacted with bidentates, or with CS<sub>2</sub> and active methylenes under PTC conditions to afford the corresponding spiro compounds **4a–h** or **5a–e**. 5-ethoxymethylene-3-phenyl-2-thioxo-4-thiazolidinone **3** was treated with diamino or aminomercapto compounds to give the desired products **6a–d**. Treatment of compound **3** with malononitrile gave compound **7**. Reaction of compound **7** with some active methylenes affords the corresponding spiro cyclopentenones **8a–c**.

**Keywords:** dibromo-4-thiazolidinone derivatives; 5-ethoxymethylene-4-thiazolidinone derivatives; dithietane; spiropentene

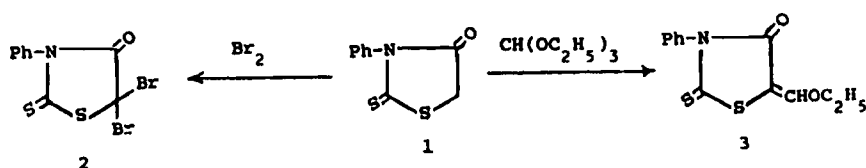
## INTRODUCTION

In connection with previous work<sup>1–4</sup> on the application of phase-transfer catalysis in heterocyclic synthesis, the synthesis of spiro heterocyclic compounds containing 4-thiazolidinone moiety is reported.

## RESULTS AND DISCUSSION

Reaction of 3-phenyl-2-thioxo-4-thiazolidinone (3-phenylrhodanine)<sup>1</sup> **1** with bromine in 1:2 molar ratio at room temperature in chloroform or with triethyl orthoformate in equimolar ratio in refluxing acetic anhydride affords 5,5-dibromo-3-phenyl-2-thioxo-4-thiazolidinone **2** or 5-ethoxy-methylene-3-phenyl-2-thioxo-4-thiazolidinone **3**, respectively. <sup>1</sup>H-NMR spectra of compounds **2** and

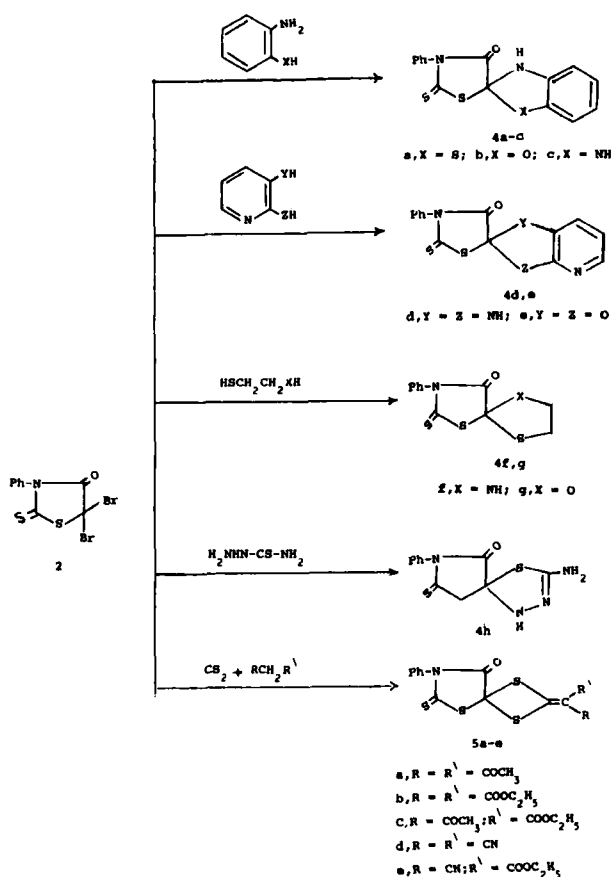
**3** showed the disappearance of the methylene group of the rhodanine nucleus and the appearance of new peaks at 8.25, 3.85-3.45 and 1.25-9.00 ppm due to =CH, OCH<sub>2</sub> and CH<sub>3</sub> respectively in the case of compound **3**.



Compound **2** was investigated as starting material for the synthesis of spiro heterocyclic systems under phase-transfer catalysis conditions (PTC) using a liquid-solid, two-phase system (dioxan/K<sub>2</sub>CO<sub>3</sub>) in the presence of tetrabutylammonium bromide (TBAB) as catalyst. Compound **2** was allowed to react with 2-aminothiophenol, 2-aminophenol, *o*-phenylenediamine, 2,3-diaminopyridine, 2,3-dihydroxypyridine, cystamine, 2-mercaptoethanol, or thiosemicarbazide, to yield the corresponding spiro compounds **4a-h** (cf Scheme I, Table I). The <sup>1</sup>H-NMR showed the presence of the 9 protons of the aromatic moieties in addition to the peaks due to NH groups for compounds **4a-d**. The spectral data of compounds **4f,g** were in agreement with the proposed structures where the <sup>1</sup>H-NMR showed a multiple peak corresponding to -CH<sub>2</sub>-CH<sub>2</sub>- group in addition to a peak corresponding to NH group in case of **4f**. The IR spectra of compound **4h** revealed the absorption bands corresponding to NH<sub>2</sub> and NH groups at 3360, 3320, 3259 cm<sup>-1</sup>. The <sup>1</sup>H-NMR showed the peaks of all hydrogen sets of the expected compounds (cf. Table I).

Using the PTC technique compound **2** was treated with carbon disulfide and different active methylenes, namely, acetylacetone, diethylmalonate, ethyl acetoacetate, malononitrile, or ethyl cyanoacetate, to afford the corresponding spiro dithietane derivatives **5a-e** respectively (cf Scheme I, Table I). The reaction pathway was assumed to proceed via two catalytic cycles. The first step, namely proton abstraction, takes place on the surface of solid carbonate. The formed anion then migrates as an ion pair with the catalyst cation into the organic phase where the second step concerned with the substitution reaction takes place in order of reactivity S<sup>-</sup> > N<sup>-</sup> > O<sup>-</sup> (cf Fig 1). The IR spectra of compounds **5a-e** showed the absorption bands corresponding to C=O and CN groups and the <sup>1</sup>H-NMR spectra were consistent with the proposed structures (cf. Table I).

On stirring compound **3** with piperazine, *p*-phenylenediamine, 2,6-diaminopyridine or cystamine in ethanol, the corresponding products **6a-d** were obtained (cf Scheme II, Table I). The <sup>1</sup>H-NMR spectra of compounds **6a,d**



SCHEME 1

showed the absence of  $-\text{OCH}_2\text{CH}_3$  and the appearance of new  $2-\text{CH}_2\text{CH}_2$  groups of compound **6a**, and NH group and  $-\text{CH}_2\text{CH}_2-$  for compound **6d** whereas the  $^1\text{H-NMR}$  and IR spectra of compounds **6b,c** revealed the presence of 2 NH groups (cf. Table I).

When compound **3** was reacted with malononitrile in refluxing acetic anhydride, the corresponding 5-malonitrilemethylene-3-phenyl-2-thioxo-4-thiazolidinone **7** was obtained. The IR spectra showed an absorption band at  $2219\text{ cm}^{-1}$  for CN groups and the  $^1\text{H-NMR}$  spectra revealed the disappearance of the ethoxy group and the presence of two peaks at 8.40 and 4.65 ppm due to  $=\text{CH}-$  and  $\text{CH}(\text{CN})_2$  respectively.

TABLE I Analytical and spectral data of the prepared compounds

Product No.	M.P. <sup>a</sup> (Cryst. Solv.)	Yield %	Mol. Form. (Mol.Wt.)	Analytical Data <sup>b</sup>		
				C	H	N
2	151	75	C <sub>9</sub> H <sub>5</sub> Br <sub>2</sub> NOS <sub>2</sub> (367.10)	29.45	1.37	3.82
	(Pet. ether 40–60)			29.31	1.50	3.64
3	134	92	C <sub>12</sub> H <sub>11</sub> NO <sub>2</sub> S <sub>2</sub> (265.36)	54.43	4.18	5.28
	(Ethanol)			54.25	4.31	5.41
4a	300	82	C <sub>15</sub> H <sub>10</sub> N <sub>2</sub> OS <sub>3</sub> (330.46)	54.52	3.05	8.48
	(Ethanol-dioxan)			54.73	3.16	8.35
4b	160	81	C <sub>15</sub> H <sub>10</sub> N <sub>2</sub> O <sub>2</sub> S <sub>2</sub> (314.39)	57.31	3.21	8.91
	(Ethanol-dioxan)			57.53	3.31	8.78
4c	115	83	C <sub>15</sub> H <sub>11</sub> N <sub>3</sub> OS <sub>2</sub> (313.41)	57.49	3.54	13.41
	(aq. dioxan)			57.38	3.46	13.29
4d	255	86	C <sub>14</sub> H <sub>10</sub> N <sub>4</sub> OS <sub>2</sub> (314.39)	53.49	3.21	17.82
	(Methanol-dioxan)			53.64	3.12	17.69
4e	186	81	C <sub>14</sub> H <sub>8</sub> N <sub>2</sub> O <sub>3</sub> S <sub>2</sub> (316.35)	53.16	2.55	8.86
	(aq. dioxan)			53.07	2.64	8.74
4f	88	89	C <sub>11</sub> H <sub>10</sub> N <sub>2</sub> OS <sub>3</sub> (282.41)	46.79	3.57	9.92
	(Methanol-dioxan)			46.66	3.44	9.80
4g	124	76	C <sub>11</sub> H <sub>9</sub> NO <sub>2</sub> S <sub>3</sub> (283.40)	46.62	3.20	4.94
	(Methanol-dioxan)			46.75	3.30	4.81
4h	265	79	C <sub>10</sub> H <sub>8</sub> N <sub>4</sub> OS <sub>3</sub> (296.40)	40.53	2.72	18.90
	(Ethanol-dioxan)			40.39	2.64	18.78
5a	108	74	C <sub>15</sub> H <sub>11</sub> NO <sub>3</sub> S <sub>4</sub> (381.52)	47.72	2.91	3.67
	(aq. dioxan)			47.61	2.80	3.78
5b	96	72	C <sub>17</sub> H <sub>15</sub> NO <sub>3</sub> S <sub>4</sub> (441.57)	46.24	3.42	3.17
	(aq. dioxan)			46.15	3.33	3.06
5c	102	75	C <sub>16</sub> H <sub>13</sub> NO <sub>4</sub> S <sub>4</sub> (411.55)	46.70	3.18	3.40
	(dioxan)			46.82	3.27	3.32
5d	180	79	C <sub>13</sub> H <sub>5</sub> N <sub>3</sub> OS <sub>4</sub> (347.82)	44.89	1.55	12.08
	(dioxan)			44.97	1.62	12.15
5e	237	85	C <sub>15</sub> H <sub>10</sub> N <sub>2</sub> O <sub>3</sub> S <sub>4</sub> (395.52)	45.55	2.55	7.08
	(dioxan)			45.68	2.47	7.11
6a	300	76	C <sub>24</sub> H <sub>20</sub> N <sub>4</sub> O <sub>2</sub> S <sub>4</sub> (524.72)	54.94	3.84	10.68
	(Methanol-acetone)			54.85	3.76	10.55
6b	300	74	C <sub>26</sub> H <sub>18</sub> N <sub>4</sub> O <sub>2</sub> S <sub>4</sub> (546.72)	57.12	3.32	10.25
	(Ethanol-acetone)			57.04	3.41	10.14
6c	242	77	C <sub>25</sub> H <sub>17</sub> N <sub>3</sub> O <sub>2</sub> S <sub>4</sub> (557.71)	53.84	3.07	12.56
	(Ethanol-acetone)			53.96	3.16	12.43
6d	206	80	C <sub>22</sub> H <sub>17</sub> N <sub>3</sub> O <sub>2</sub> S <sub>5</sub> (515.73)	51.24	3.32	8.15
	(Ethanol-acetone)			51.39	3.41	8.24
7	142	76	C <sub>12</sub> H <sub>7</sub> N <sub>3</sub> OS <sub>2</sub> (285.85)	54.63	2.64	14.70
	(Ethanol)			54.79	2.52	14.59
8a	214	65	C <sub>18</sub> H <sub>15</sub> N <sub>3</sub> O <sub>3</sub> S <sub>2</sub> (385.47)	56.09	3.92	10.90
	(Ethanol)			56.21	3.81	10.79
8b	172	62	C <sub>19</sub> H <sub>17</sub> N <sub>3</sub> O <sub>4</sub> S <sub>2</sub> (415.50)	54.49	4.12	10.11
	(Ethanol)			54.58	4.24	10.01
8c	220	63	C <sub>20</sub> H <sub>19</sub> N <sub>3</sub> O <sub>5</sub> S <sub>2</sub> (445.53)	53.92	4.30	9.43
	(Ethanol)			53.84	4.21	9.55

TABLE I Continued

Product No.	IR (KBr) <sup>c</sup> $\nu(\text{cm}^{-1})$	H-NMR (DMSO- $d_6$ ) <sup>d</sup> $\delta(\text{ppm})$
2	1710(C=O); 1145(C=S); 548(C-Br)	7.85-7.25(m, 5H, arom.)
3	1705(C=O); 1148(C=S); 1105(C-O-C)	8.25(s, 1H, =CH); 7.85-7.25(m, 5H, arom.); 3.85-3.45(q, 2H, CH <sub>2</sub> ); 1.25-(t, 3H, CH <sub>3</sub> ).
4a	3320(NH); 1712(C=O); 1140(C=S)	10.75(s, 1H, NH); 7.90-7.20(m, 9H, arom.).
4b	3305(NH); 1709(C=O); 1143(C=S).	10.25(s, 1H, NH); 7.95-7.25(m, 9H, arom.).
4c	3316, 3312(2NH); 1712(C=O); 1148(C=S).	10.75(s, 1H, NH); 7.90-7.20(m, 9H, arom.).
4d	3330, 3327(2NH); 1709(C=O); 1140(C=S).	10.40(br, 2H, 2NH); 8.05-7.20(m, 8H arom. + pyr.).
4e	1703(C=O); 1149(C=S).	8.05-7.25(m, 8H, arom. + pyr.).
4f	3302(NH); 1702(C=O); 1145(C=S).	11.30(s, 1H, NH); 7.80-7.20(m, 5H, arom.); 3.35-2.80(m, 4H, 2CH <sub>2</sub> ).
4g	1709(C=O); 1140(C=S).	11.15(s, 1H, NH); 7.25-7.10(m, 5H, arom.); 3.30-2.80(m, 4H, 2CH <sub>2</sub> ).
4h	3360, 3320, 3259(NH <sub>2</sub> , NH); 1708(C=O); 1145(C=S).	10.95(s, 1H, NH); 7.90-7.25(m, 5H, arom.); 6.20(s, 2H, NH <sub>2</sub> ).
5a	1720, 1710(C=O); 1147(C=S).	7.85-7.25(m, 5H, arom.); 2.55(s, 6H, 2CH <sub>3</sub> ).
5b	1728, 1710(C=O); 1143(C=S).	7.90-7.20(m, 5H, arom.); 4.35-3.95(q, 4H, 2CH <sub>2</sub> ); 1.40-1.15(s, 6H, 2CH <sub>3</sub> ).
5c	1730, 1718, 1705(C=O); 1148(C=S).	7.85-7.20(m, 5H, arom.); 4.30-3.95(q, 2H, CH <sub>2</sub> ); 2.60(s, 3H, CH <sub>3</sub> ); 1.35-1.10(t, 3H, CH <sub>3</sub> ).
5d	2219(C=N); 1710(C=O); 1144(C=S).	7.90-7.25(m, 5H, arom.)
5e	2220(C=N); 1726, 1705(C=O); 1148(C=S).	7.85-7.20(m, 5H, arom.); 4.35-3.90(q, 2H, CH <sub>2</sub> ); 1.35-1.15(t, 3H, CH <sub>3</sub> ).
6a	1705(C=O); 1142(C=S).	8.35(s, 2H, 2=CH); 8.05-7.20(m, 10H, arom.); 3.65-2.85(br, 8H, piperazine).
6b	3351(NH); 1702(C=O); 1147(C=S).	11.20(br, 2H, 2NH); 8.30(s, 2H, 2=CH); 8.05-7.15(m, 14H, arom.).
6c	3362(NH); 1704(C=O); 1149(C=S).	11.35(br, 2H, 2NH); 8.35(s, 2H, 2=CH); 8.00-7.20(m, 13H, arom. + pyr.).
6d	3340(NH); 1703(C=O); 1147(C=S).	8.35(s, 2H, 2=CH); 7.85-7.15(m, 10H, arom.); 3.40-2.85(m, 4H, 2CH <sub>2</sub> ).
7	2219(C-N); 1708(C=O); 1140(C=S).	8.40(s, 1H, =CH); 7.85-7.25(m, 5H, arom.); 4.65(s, 1H, CH).
8a	3372, 3275(NH <sub>2</sub> ); 2219(C-N); 1723, 1703(C=O); 1149(C=S).	7.80-7.20(m, 5H, arom.); 4.85(s, 2H, NH <sub>2</sub> ); 3.15(s, 2H, CH <sub>2</sub> ); 2.60(s, 6H, 2CH <sub>3</sub> ).
8b	3376, 3273(NH <sub>2</sub> ); 2221 (C-N); 1725, 1722, 1706(C=O); 1149(C=S).	7.85-7.20(m, 5H, arom.); 4.90(s, 2H, NH <sub>2</sub> ); 4.30-3.95(q, 2H, CH <sub>2</sub> ); 3.20(s, 2H, CH <sub>2</sub> ); 2.55(s, 3H, CH <sub>3</sub> ); 1.30-1.15(t, 3H, CH <sub>3</sub> ).
8c	3369, 3271(NH <sub>2</sub> ); 2223(C-N); 1728, 1705, 1706(C=O); 1149(C=S).	7.80-7.20(m, 5H, arom.); 4.85(s, 2H, NH <sub>2</sub> ); 4.35-3.95(q, 4H, 2CH <sub>2</sub> ); 3.25(s, 2H, CH <sub>2</sub> ); 1.30-1.05(t, 6H, 2CH <sub>3</sub> ).

<sup>a</sup>Uncorrected<sup>b</sup>Satisfactory microanalyses obtained C:  $\pm 0.35\%$  H:  $\pm 0.40\%$  N: 0.20% Measured by Nicolet FT-IR 710 Spectrophotometer Measured by a Varian EM 360 L Spectrometer at 60 MHz using TMS as internal standard.

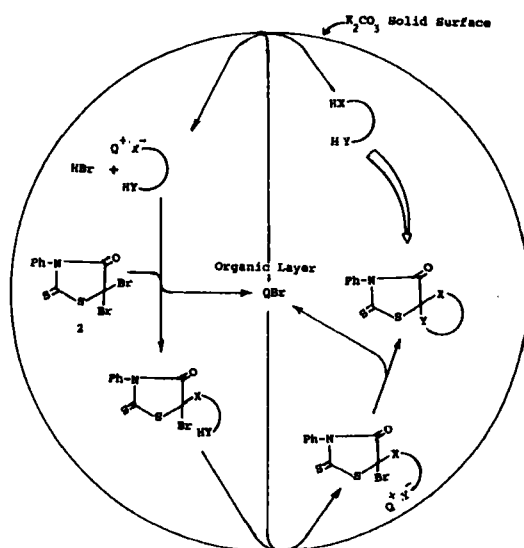


FIGURE 1

Compound **7** was proven to be an excellent precursor for the synthesis of spiro cyclopentene derivatives **8a-c** when reacted with acetylacetone, ethyl acetoacetate, or diethyl malonate, respectively. The IR spectra showed the presence of  $\text{NH}_2$  and  $\text{CN}$  groups in addition to  $\text{C}=\text{O}$  group and the  $^1\text{H-NMR}$  spectra were in agreement with the proposed structures (cf, Scheme II, Table I).

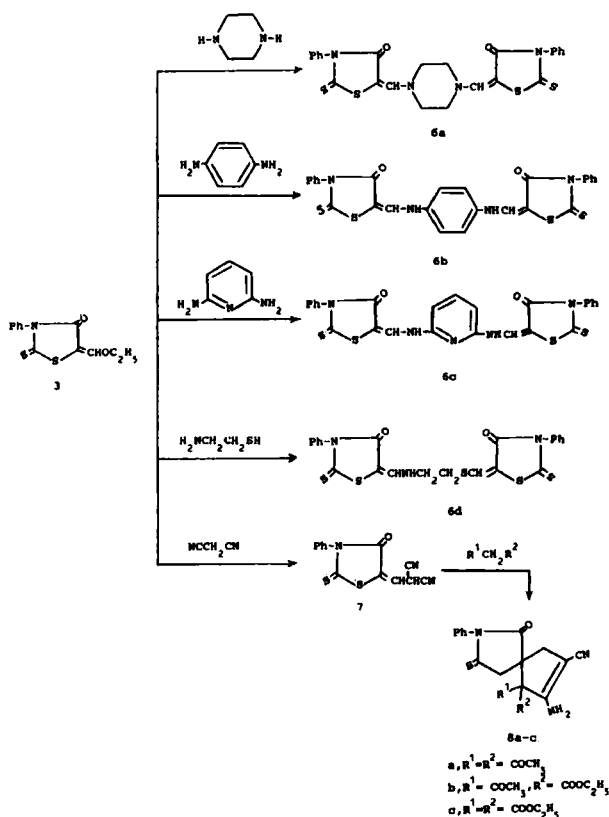
## Experimental

### *Synthesis of 5,5-dibromo-3-phenyl-2-thioxo-4-thiazolidinone 2*

A solution of compound **1** (0.02 mol) in chloroform (25 ml) was added dropwise to a solution of bromine (0.04 mol) in chloroform (30 ml) with stirring over 45 minutes. The reaction mixture was stirred for an additional 2 hr. The solvent was evaporated *in vacuo*. The residual solid was crystallized from petroleum ether (40–60°C).

### *Synthesis of 5-ethoxymethylene-3-phenyl-2-thioxo-4-thiazolidinone 3*

A mixture of compound **1** (0.02 mol) and triethyl orthoformate (0.022 mol) was refluxed in acetic anhydride (20 ml) for 4 hr. The reaction mixture was poured into ice cold water (500 ml). The precipitated solid was collected by filtration and crystallized from ethanol.



SCHEME 2

### Synthesis of compounds 4a-h. General procedure

A mixture of compound 2 (0.002 mol), a proper amino compound (0.002 mol) anhydrous potassium carbonate (3 g.), a catalytic amount of tetrabutylammonium bromide (TBAB), and dry dioxan (30 ml) was stirred for 3 hr. The reaction mixture filtered off, and the filtrate was evaporated *in vacuo*. The residual solid was washed with water, triturated with petroleum ether (60–80 °C), and crystallized (cf Table I).

### Synthesis of compounds 5a-e. General procedure

A mixture of a proper active methylene (0.02 mol), CS<sub>2</sub> (0.02 mol), anhydrous potassium carbonate, a catalytic amount of TBAB, and chloroform (50 ml) was stirred for 15 minutes at 60°C. To the formed dianionic ambident was added to



compound **2** (0.02 mol). The reaction mixture was stirred for 2 hr, then filtered off, and the organic layer was washed with water, dried over anhydrous sodium sulfate, and evaporated *in vacuo*. The residue was triturated with petroleum ether (60–80°C) and crystallized (cf Table I).

#### ***Synthesis of compounds 6a–d. General procedure***

To a solution of compound **2** (0.006 mol) in absolute ethanol (40 ml) was added the proper amine. The reaction mixture was stirred for 4 hr. The separated solid was collected by filtration and crystallized (cf Table I).

#### ***Synthesis of 5-malononitrilemethylene-3-phenyl-2-thioxo-4-thiazolidinone 7***

An equimolar amount (0.03 mol) of compound **3** and malononitrile in acetic anhydride (30 ml) was refluxed for 4 hr. The reaction mixture was poured into ice cold water (500 ml). The precipitate was collected by filtration and crystallized (cf Table I).

#### ***Synthesis of compounds 8a–c. General procedure***

To a solution of compound **7** (0.003 mol) in absolute ethanol (20 ml) was added the proper active methylene (0.003 mol) and a catalytic amount of piperidine. The reaction mixture was refluxed for 3 hr. The solvent was evaporated *in vacuo*. The separated solid was washed with water, triturated with petroleum ether (60–80°C), and crystallized (cf Table I).

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