SYNTHESIS OF LUMINOPHORIC DERIVATIVES OF PBD BASED ON 2,5-DIARYL SUBSTITUTED THIAZOLES AND OXAZOLES

Pavel LHOTÁK and †Antonín KURFÜRST

Department of Organic Chemistry,
Prague Institute of Chemical Technology, 166 28 Prague 6

Received December 14, 1992
Accepted January 26, 1993

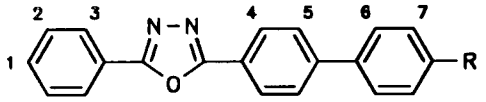
Dedicated to Professor Otto Wichterle on the occasion of his 80th birthday.

The Friedel–Crafts acylation of 2-(biphenyl-4-yl)-5-phenyl-1,3,4-oxadiazole (PBD) with hippuryl chloride has been used to prepare the derivative *V* which on cyclization with $POCl_3$ or P_4S_{10} gives the respective oxazole (or thiazole) derivative of PBD, *XIa* or *XIb*. The reaction of carboxylic acid *II* with 4-(ω-aminoacetyl)biphenyl in the presence of CDI gives *N*-acyl-α-aminoketone *VII*; the analogous compound *VI* has been prepared by acylating ω-aminoacetophenone with acyl chloride *III*. The cyclization of these compounds gives bifluorophores *Xa* – *Xd*.

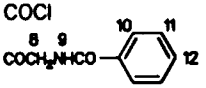
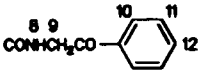
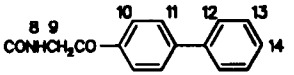
An interesting group of luminescent compounds includes the so-called bifluorophores formed by the combination of two simple fluorophoric fragments. It is known[1] that substances of the type of diaryloxazoles or thiazoles and diaryloxadiazoles belong among very efficient fluorophores. Continuing our earlier studies[2-4] of luminophoric substances based on PBD (*I*) derivatives, we have tried to prepare bifluorophoric systems formed by combining the above-mentioned luminophores, i.e. the diaryloxadiazole and diaryloxa(thia)zole fluorophores.

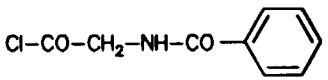
We synthetized compounds *VI* and *VII* as the precursors for preparing the derivatives *Xa* – *Xd* based on PBD. Compound *VI* was obtained by the acylation of ω-aminoacetophenone *IXa* with acyl chloride *III*. The analogous reaction with 4-aminoacetylbiphenyl failed, therefore compound *VII* was obtained by treating the carboxylic acid *II* with carbonyldiimidazole followed by the reaction with derivative *IXb*. The required ω-aminoacetyl derivatives were prepared from the starting bromoacetyl derivatives and urotropin[5,6] and subsequent decomposition of the urotropinium[5,7] salts *VIII*. The derivative *V* was obtained by the Friedel–Crafts acylation of PBD with hippuryl chloride *IV* in CS_2 solution with $AlCl_3$ as a catalyst. The reaction is regioselective[8] and gives a single product formed by the substitution at 4'-position of biphenyl section of PBD molecule.

The oxazole derivatives *Xa*, *Xb* and *XIa* were prepared by the cyclization of the corresponding *N*-acyl-α-aminoketones *V* – *VII* with $POCl_3$, the thiazoles *Xc*, *Xd* and

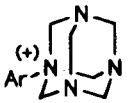


I – III, V – VII

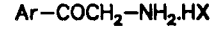
	R
I	H
II	COOH
III	COCl
V	
VI	
VII	



IV

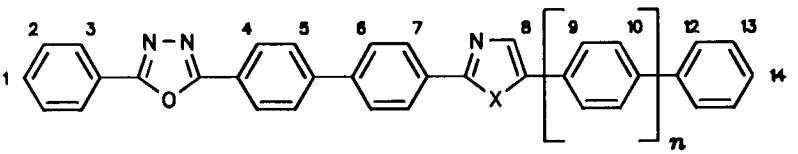


VIII



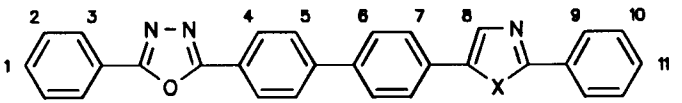
IX

In formulae *VIIIa*, *IXa* : Ar = phenyl;
VIIIb, *IXb* : Ar = biphenyl-4-yl



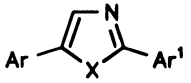
X

	X	*n*		X	*n*
Xa	O	0	*Xc*	S	0
Xb	O	1	*Xd*	S	1



	X
XIa	O
XIb	S

XI



XII

	Ar	Ar[1]	X
XIIa	Ph	Ph	O
XIIb	Biph	Ph	O
XIIc	Ph	Biph	O
XIId	Biph	Biph	O
XIIe	Ph	Ph	S

XIb were obtained by the analogous reaction of the derivatives *V – VII* with the Lawesson reagent[9] (Table I). Using phosphorus pentasulfide instead of the Lawesson reagent gave a mixture of the oxazole and thiazole derivatives whose composition depends on the reaction time and solvent (temperature). As a consequence of the minimum differences in the R_F values of these compounds the reaction mixture was practically inseparable and was used only for preparing the derivative *Xd*.

The structure of all the compounds prepared was proved by elemental analysis, IR, NMR spectra, and/or MS (Tables II – IV). The ^{1}H NMR spectra of compounds *X* and *XI* exhibit characteristic signals of the PBD residue in which the chemical shifts of the protons H-1,2 (≈ 7.56 ppm) and H-3 (≈ 8.17 ppm) remain practically independent of the type of heteroatom and/or the type of substitution of oxa-/thiazole ring. The protons H-4 through H-7 form subspectra of the AA'XX' type which, under the conditions of measurement ($CDCl_3$, 20 °C), were interpreted as simple systems of A_2X_2 doublets. As it follows from Table III the signals of H-4 (≈ 8.25 ppm) and H-5 (≈ 7.83 ppm) do not significantly change their positions in the spectra because of the large distance from the

TABLE I
Reaction conditions for preparation of compounds *X* and *XI*

Compound	Starting ketone	Reaction time, h	Yield, %	M.p., °C
Xa	*VI*	3	76	238 – 239
Xb	*VII*	9	70	261 – 263
XIa	*V*	1.5	94	228 – 229
Xc	*VI*	14	43	216.5 – 218/297 – 298[a]
Xd[b]	*VII*	30	25	259 – 261.5/>360[c]
XIb	*V*	14	50	211 – 213/251 – 255[a]

[a] Dioxane; [b] the product was obtained by refluxing 0.6 mmol diketone with 2 g P_4S_{10}; [c] $CHCl_3$.

position of substitution. As for the signal of proton H-8 of the heterocyclic ring[4] it exhibits a marked upfield shift with compounds *Xc*, *Xd* (≈ 0.55 ppm) as compared with the corresponding oxazole derivatives *Xa*, *Xb*. The same is also true of the pair of derivatives *XIa*, *XIb*. The substitution of phenyl by biphenylyl residue has no distinct effect on the shift of this signal (cf., e.g., *Xa* and *Xb*). All the signals in ^{1}H NMR spectra of the compounds discussed were assigned on the basis of 2D COSY experiments.

The UV spectra of compounds *X* and *XI* show a bathochromic shift (by as much as 30 nm) of the absorption maximum as compared with both the PBD molecule and analogous derivatives of thiazoles and oxazoles *XII* (refs[10,11]) (Table V). A similar phenomenon can also be observed in the fluorescence spectra of compounds *X* and *XI*, where a combination of two simple fluorophores produces a system with the absorption maximum shifted to higher wavelengths by as much as 50 nm as compared with the maxima of both parent fluorophores. The extending of system of aromatic rings by another phenyl group (e.g. *Xa* and *Xb*) results in an indistinct bathochromic shift in both absorption and emission spectra. The same effect results from substituting the oxygen atom (oxazole derivatives *Xa*, *Xb*, *XIa*) by sulfur in analogous thiazole derivatives *Xc*, *Xd*, *XIb*.

An interesting phenomenon is the double melting points observed in some cases (compounds *VI*, *VII*, *Xc*, *Xd* and *XIb*), the phenomenon being repeatedly observed after solidification of melt. With regard to the presence of relatively long molecular symmetry axis, this phenomenon could be due to potential liquid-crystalline properties of the derivatives mentioned.

TABLE II
^{1}H NMR spectra of compounds *V* – *VII* ($CDON(CD_3)_2$, 20 °C)

Compound	δ, ppm/*J*, Hz						
	1,2	3	4	5	6	7	8
V[a]	7.65 m	8.20 m	8.29 d *J* = 8.2	8.03 d *J* = 8.4	7.97 d *J* = 8.5	8.20 d *J* = 8.1	4.94 d *J* = 5.5
VI[b]	7.64 m	8.18 m	8.27 d *J* = 8.3	8.00 d *J* = 8.00	7.89 d *J* = 7.89	8.11 d *J* = 8.11	8.45 s
VII[c]	7.55 m	8.17 m	8.25 d *J* = 8.10	7.81 d *J* = 8.05	7.76 m	8.12 d *J* = 8.05	7.32 s

[a] 8.44 s (H-9); 8.00 d, *J* = 7.6 (H-10); 7.49 t, *J* = 7.4 (H-11); 7.55 t, *J* = 7.2 (H-12); [b] 4.93 d, *J* = 5.5 (H-9); 8.07 d, *J* = 7.3 (H-10); 7.55 t, *J* = 7.6 (H-11); 7.64 m (H-12); [c] 5.01 s (H-9); 8.02 d, *J* = 8.02 (H-10); 7.76 m (H-11); 7.64 d, *J* = 7.64 (H-12); 7.48 t, *J* = 7.37 (H-13); 7.42 m (H-14); measured in $CDCl_3$.

EXPERIMENTAL

The melting points were determined with a Boetius apparatus and are not corrected. The IR spectra were measured with a Perkin–Elmer 325 spectrophotometer. The ^{1}H NMR spectra were obtained with the use of a Bruker AM 400 apparatus (400 MHz) using tetramethylsilane as the internal standard (δ = 0.00 ppm). The electronic absorption spectra were measured on a Perkin–Elmer 330 spectrophotometer. The fluorescence excitation and emission spectra were measured on a spectrofluorimeter Perkin–Elmer MPF-44B. The mass spectra were obtained by the field desorption method using a JEOL DX 303/DA 5000 apparatus.

The purity of the substances prepared and the reaction courses were followed by means of TLC using Silufol and Alufol plates (Kavalier, Sázava). The detection was carried out in iodine vapours or under UV light.

The compounds *II* and *III* were prepared by known procedures[2,3].

TABLE III
^{1}H NMR spectra of compounds *X* and *XI* ($CDCl_3$, 20 °C)

Compound	δ, ppm/*J*, Hz							
	1,2	3	4	5	6	7	8	9
Xa[a]	7.57 m	8.18 m	8.25 d *J* = 8.55	7.83 d *J* = 8.40	7.79 d *J* = 8.43	8.23 d *J* = 8.41	7.50 s	7.76 d *J* = 6.17
Xa[b,c]	7.65 m	8.15 m	8.24 d *J* = 8.24	8.02 d *J* = 8.16	7.98 d *J* = 8.09	8.21 d *J* = 8.24	7.81 s	7.85 d *J* = 7.82
Xb[d]	7.56 m	8.17 m	8.25 d *J* = 8.46	7.83 d *J* = 8.49	7.79 d *J* = 8.50	8.24 d *J* = 8.47	7.51 s	7.82 d *J* = 8.43
Xc[e]	7.56 m	8.16 m	8.23 d *J* = 8.52	7.81 d *J* = 8.54	7.75 d *J* = 8.50	8.09 d *J* = 8.46	8.04 s	7.62 d *J* = 7.06
Xd[f]	7.55 m	8.17 m	8.24 d *J* = 8.53	7.82 d *J* = 8.54	7.76 d *J* = 8.51	8.11 d	8.10 s	7.70 d *J* = 8.62
XIa[g]	7.65 m	8.19 m	8.27 d *J* = 8.3	8.00 d *J* = 8.4	7.93 d *J* = 8.4	8.01 d *J* = 8.5	7.81 s	8.16 d *J* = 8.2
XIb[h]	7.57 m	8.18 m	8.25 d *J* = 8.56	7.81 d *J* = 8.58	7.73 m	7.73 m	8.10 s	7.99 d *J* = 8.06

[a] 7.47 t, *J* = 7.57 (H-10); 7.39 t, *J* = 7.29 (H-11). [b] $SO(CD_3)_2$. [c] 7.52 t, *J* = 7.61 (H-10); 7.40 t, *J* = 7.21 (H-11). [d] 7.70 d, *J* = 8.45 (H-10); 7.64 d, *J* = 7.90 (H-12); 7.46 t, *J* = 7.96 (H-13); 7.39 t, *J* = 7.29 (H-14). [e] 7.43 t, *J* = 7.15 (H-10); 7.35 t, *J* = 7.35 (H-11). [f] 7.66 d, *J* = 8.57 (H-10); 7.63 d, *J* = 7.76 (H-12); 7.46 t, *J* = 7.8 (H-13); 7.37 t, *J* = 7.33 (H-14). [g] $CDON(CD_3)_2$, 7.57 m (H-10,11). [h] 7.48 m (H-10,11).

Hippuryl Chloride (*IV*)

A mixture of finely powdered hippuric acid (54 g, 0.30 mol), powdered PCl_5 (85 g, 0.408 mol), and 205 ml fresh redistilled acetyl chloride was intensively shaken in a closed 1 000 ml flask, the liberated HCl being let out every 10 min. After 3.5 h, the precipitate formed was filtered without access of air, washed with 3 × 100 ml dry hexane, and dried at room temperature in vacuum (oil pump). Yield: 69.1 g light brown powder which was immediately used in subsequent reaction. After standing several days in dessiccator over P_2O_5 the product changes its colour to brown to black and becomes inefficient in the Friedel–Crafts acylation.

4'-[(Benzoylaminomethyl)carbonyl]-4-(5-phenyl-1,3,4-oxadiazol-2-yl)biphenyl (*V*)

A suspension of PBD (*I*, 10 g, 3.35 . 10^{-2} mol) and hippuryl chloride (*IV*, 19.87 g, 0.100 mol) in 250 ml carbon disulfide was treated with $AlCl_3$ (53.6 g, 0.402 mol) added during 1 h at room tem-

TABLE IV
Elemental analyses and IR spectra of newly prepared compounds

Compound	Formula (M.w.)	IR ν, cm^{-1}	Calculated/Found		
			% C	% H	% N
V	$C_{29}H_{21}N_3O_3$	3 420 s, 2 910 w	75.79	4.61	9.15
	(459.5)	1 690 s, 1 652 s	75.58	4.70	9.21
VI	$C_{29}H_{21}N_3O_3$	3 420 s, 2 910 w	75.79	4.61	9.15
	(459.5)	1 690 s 1 652 s	75.58	4.70	9.21
VII	$C_{35}H_{25}N_3O_3$	3 360 s, 1 685 s	78.48	4.71	7.85
	(535.6)	1 630 s, 1 601 s	78.51	4.91	7.75
Xa	$C_{29}H_{19}N_3O_2$	1 610 s, 1 547 s	78.89	4.35	9.52
	(441.5)	1 480 s, 1 445 m	78.79	4.52	9.31
Xb	$C_{35}H_{23}N_3O_2$	1 605 s, 1 563 s	81.21	4.49	8.12
	(517.6)	1 540 s, 1 480 s	81.19	4.63	8.00
Xc	$C_{29}H_{19}N_3OS$	1 610 s, 1 546 s	76.12	4.19	9.19
	(457.6)	1 480 s, 1 448 s	75.94	4.41	8.94
Xd	$C_{35}H_{23}N_3OS$	1 610 w, 1 544 m		532 $(M - 1)^+$	
	(533.7)	1 480 s, 1 545 w			
XIa[a]	$C_{29}H_{19}N_3O_2$	1 610 s, 1 550 s	78.89	4.35	9.52
	(441.5)	1 488 s, 1 450 s	78.77	4.50	9.40
XIb[b]	$C_{29}H_{19}N_3OS$	1 546 s, 1 480 s	76.12	4.19	9.19
	(457.6)	1 448 s	76.57	4.31	8.71

[a] S calculated/found: 7.01%/7.41%; [b] S calculated/found: 7.01%/6.77%.

perature, whereafter the mixture was refluxed 5.5 h. After decomposition with dilute HCl and ice, the precipitate formed was collected by filtration and recrystallized from DMF to give 7.23 g (47%) product melting at 236 – 242 °C. A part thereof was submitted to column chromatography (SiO_2, $CHCl_3$–acetone 5 : 1), the respective fractions were combined and evaporated, and the residue was recrystallized from $CHCl_3$ to give product *V*, m.p. 242 – 244 °C.

4'-[(Benzoylmethyl)aminocarbonyl]-4-(5-phenyl-1,3,4-oxadiazol-2-yl)biphenyl (*VI*)

A solution of hydrobromide of ω-aminoacetophenone *IXa* (0.32 g, 1.46 10^{-3} mol) in 20 ml water was added dropwise to a solution of acyl chloride *III* (0.5 g, 1.46 . 10^{-3} mol) in 100 ml $CHCl_3$. After adding 0.25 g ammonium acetate, the reaction mixture was stirred at room temperature 12 h, whereafter it was poured into 150 g methanol. The precipitated solid was collected by suction and washed with methanol to give 0.51 g (76%) crystalline product. After two recrystallizations from a chloroform–methanol mixture it exhibited a double melting point of 235 – 238 °C and 244 – 245 °C.

4'-[(4-Phenylbenzoylmethyl)aminocarbonyl]-4-(5-phenyl-1,3,4-oxadiazol-2-yl)biphenyl (*VII*)

A solution of carbonyldiimidazole (1.61 g, 0.01 mol) in 50 ml THF was added dropwise to a refluxing suspension of acid *II* (3.4 g, 0.01 mol) in 250 ml absolute THF and the mixture was stirred at 40 °C for 1 h. At the same temperature, a suspension of 2.92 g compound *IXb* in 100 ml THF was added and the resulting mixture was stirred and refluxed 16.5 h. After three days' standing at room tem-

TABLE V
UV-VIS and fluorescence (excitation and emission) spectra of compounds *Xa* – *Xd*, *XIa*, *Xb* and some model structures

Compound	UV[a] λ (log ε)	Fluorescence			
		ex.[a]	em.[a]	ex.[b]	em.[b]
Xa	339 (4.64)	376	425	380[c], 396, 418	453
Xb	350 (4.81)	388	438	382, 396, 428	486
Xc	351 (4.75)	390	415[c], 431	380, 396, 421	464
Xd	306 (4.71)	384	420, 446	384, 397, 421	472, 496
	358 (4.46)				
XIa	342 (4.85)	372	415	382, 397, 411	445[c], 460
XIb	346 (4.76)	379	403, 423	384, 396, 420	448, 467
PBD[d]	303 (4.65)[e]		365[f]		
XIIa[g]	307 (4.41)[f]		365[f]		
XIIb[h]	323 (4.59)[e]		386[f]		
XIIc[h]	320 (4.59)[e]		392[f]		
XIId[h]	335 (4.68)[e]		410[f]		
XIIe[h]	322 (4.13)[e]		396[f]		

[a] Dichloromethane; [b] solid state; [c] inflexion; [d] ref.[1]; [e] cyclohexane; [f] toluene; [g] ref.[10]; [h] ref.[11].

perature, the precipitated solid was collected by filtration and recrystallized from a DMF–THF (2 : 1) mixture to give 2.35 g (44%) product with double melting point of 268 – 270 °C and 305 – 308 °C.

ω-Aminoacetylbenzene (*IX*)

A) Preparation of urotropinium salt VIIIa: A solution of urotropin (21.2 g, 0.15 mol) in 150 ml chloroform was added to a solution of phenacyl bromide (30 g, 0.15 mol) in 150 ml chloroform and the mixture formed was left to stand at room temperature 3 days. The precipitated solid was collected by suction and washed with CCl_4 to give 46.5 g (91%) white crystalline solid, m.p. 164 – 167 °C with decomposition (ref.[5] gives m.p. 165 °C with decomposition).

B) Decomposition of urotropinium salt: A solution of the above-described product (35 g, 0.103 mol) in a mixture of 260 ml EtOH and 45 ml concentrated HCl was left to stand at room temperature 3 days. The precipitated ammonium chloride was removed by suction and the filtrate was evaporated. The residue was recrystallized from ethanol to give 15.2 g (68% with respect to the hydrobromide) product (a mixture of hydrobromide and hydrochloride), m.p. 198 – 200 °C. The product was not purified before subsequent application.

4-(ω-Aminoacetyl)biphenyl (*IXb*)

A) Preparation of urotropinium salt VIIIb: The reaction of *p*-phenylphenacyl bromide with urotropin was carried out in the same way as in the preceding case and gave 91% product decomposing on heating above 160 °C (ref.[6] gives m.p. 153 – 154 °C with decomposition).

B) Decomposition of urotropinium salt: The procedure was the same as in the preceding case and gave 51% product with nondefined m.p. (it decomposes continuously on heating[7]) which was not purified before further application.

General Procedure of Preparation of Oxazoles *Xa*, *Xb*, *XIa*

The starting *N*-acyl-α-aminoketone *V – VII* (2 mmol) was refluxed with 40 ml $POCl_3$, whereafter the excess dehydrating agent was removed by distillation (≈ 30 ml), and the residue was poured into 250 ml water. The separated solid was collected by suction, submitted to column chromatography (SiO_2, $CHCl_3$), and recrystallized from a chloroform–methanol mixture. The reaction conditions, yields, and melting points are presented in Table I.

General Procedure of Preparation of Thiazoles *Xc*, *Xd*, *XIb*

The starting *N*-acyl-α-aminoketone (0.7 mmol) was refluxed with 0.9 mmol Lawesson agent in 50 ml xylene, whereafter the hot reaction mixture was poured through a short SiO_2 column. The solvent was evaporated and the solid residue was submitted to column chromatography (twice; SiO_2, $CHCl_3$) and recrystallized from the solvent given. The reaction and purification conditions, yields, and melting points are presented in Table I.

REFERENCES

1. Krasovitskii B. M., Bolotin B. M.: *Organicheskie lyuminofory*. Khimiya, Leningrad 1976.
2. Lhoták P., Kurfürst A., Nádeník P.: Collect. Czech. Chem. Commun. *57*, 385 (1992).
3. Kurfürst A., Kuthan J., Lhoták P., Nádeník P., Schroth W., Spitzner R.: Collect. Czech. Chem. Commun. *55*, 2722 (1990).
4. Lhoták P., Kurfürst A.: Collect. Czech. Chem. Commun. *58*, 1898 (1993).

5. Mannich C., Hahn F. L.: Chem. Ber. *44*, 1542 (1911).
6. Bahner C. T., Pickens M. D., Pickens D., Easley W. K.: J. Am. Chem. Soc. *72*, 2266 (1950).
7. Campbell K. N., Campbell B. K., Chaput E. P.: J. Org. Chem. *8*, 99 (1943).
8. Lhoták P., Kurfürst A., Nádeník P.: Collect. Czech. Chem. Commun. *56*, 1495 (1991).
9. Cherkasov R. A., Kutyrev G. A., Pudovik A. N.: Tetrahedron *41*, 2567 (1985).
10. Krasovitskii B. M., Shershukov V. M., Yagupol'skii L. M.: Khim. Geterotsikl. Soedin. *1982*, 1042.
11. Ott D. G., Hayes F. N., Hansbury E., Kerr V. N.: J. Am. Chem. Soc. *79*, 5448 (1957).

Translated by J. Panchartek.