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SYNTHESIS AND CYCLIZATION OF N-(4-PHENOXYPHENYL)-β-ALANINES

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We have used the reaction of 4-aminodiphenyl ester with acrylic, methacrylic, crotonic, and itaconic acids to synthesize N-substituted β-alanines, which undergo ring closure to form derivatives of dihydropyrimidinedione and 4-carboxy-2-pyrrolidinone. We have studied the reactions of acylation and recyclization of the dihydropyrimidinedione ring, and we have synthesized derivatives of 4-carboxy-1-(4-phenoxyphenyl)-2-pyrrolidinone: arylidene hydrazides, 2[(2-oxo-4-pyrrolidinyl-1-(4-phenoxy-phenyl)]benzimidazole.

Keywords: arylidene hydrazides, dihydropyrimidinediones, N-substituted β-alanines, 4-carboxy-2-pyrrolidinones.

Continuing studies in the area of synthesis and cyclization of N-substituted amino acids [1-4], we have developed a method for synthesis of N-(4-phenoxyphenyl)-β-alanines and we have studied their heterocyclization to form five-membered and six-membered heterocycles.

We obtained N-(4-phenoxyphenyl)-β-alanine (**2**) and its α- and β-derivatives **3, 4** by addition of 4-aminodiphenyl ester (**1**) to α,β-unsaturated acids (acrylic, methacrylic, crotonic) in 50% acetic acid. We did not isolate β-alanine **2** separately in pure form, and for synthesis of the heterocyclic systems we used the reaction mixture of the amine **1** with acrylic acid, since in this reaction a mixture is formed of two compounds that are complicated to separate: N-(4-phenoxyphenyl)-β-alanine (**2**) and N-carboxyethyl-N-(4-phenoxyphenyl)-β-alanine.

When the synthesized N-(4-phenoxyphenyl)-β-alanines **2-4** are boiled with urea in glacial acetic acid, the corresponding N-carbamoyl-N-(4-phenoxyphenyl)-β-alanines **6, 11, 15** are formed, which without isolation were treated with conc. HCl to undergo ring closure to form 2,4-(1H,3H)-dihydropyrimidinediones **8, 13, 17**. When potassium thiocyanate is used instead of urea, the corresponding 4-(1H,3H)-dihydropyrimidinone-2-thiones **9, 14, 18** are formed. The dihydropyrimidinedione ring is rather unstable in alkaline medium. Thus compounds **8, 9** are readily cleaved to form N-carbamoyl(or thiocarbamoyl)-N-(4-phenoxyphenyl)-β-alanines **6, 7** in 10% NaOH solution.

In the ^{1}H NMR spectra of dihydropyrimidinedione **8** and its 2-thio analog **9**, in addition to signals from the proton of the NH group and the aromatic protons, upfield we observe signals from the 5-CH_2 and 6-CH_2 protons as characteristic triplets. The protons of the CH and CH_2 groups of the heterocyclic moiety of the molecules for the 5- and 6-methyldihydropyrimidinediones **13, 17** and their 2-thio analogs **14, 18** form a typical AMX system, where the signals from protons of the CH_2 group appear as two doublets.

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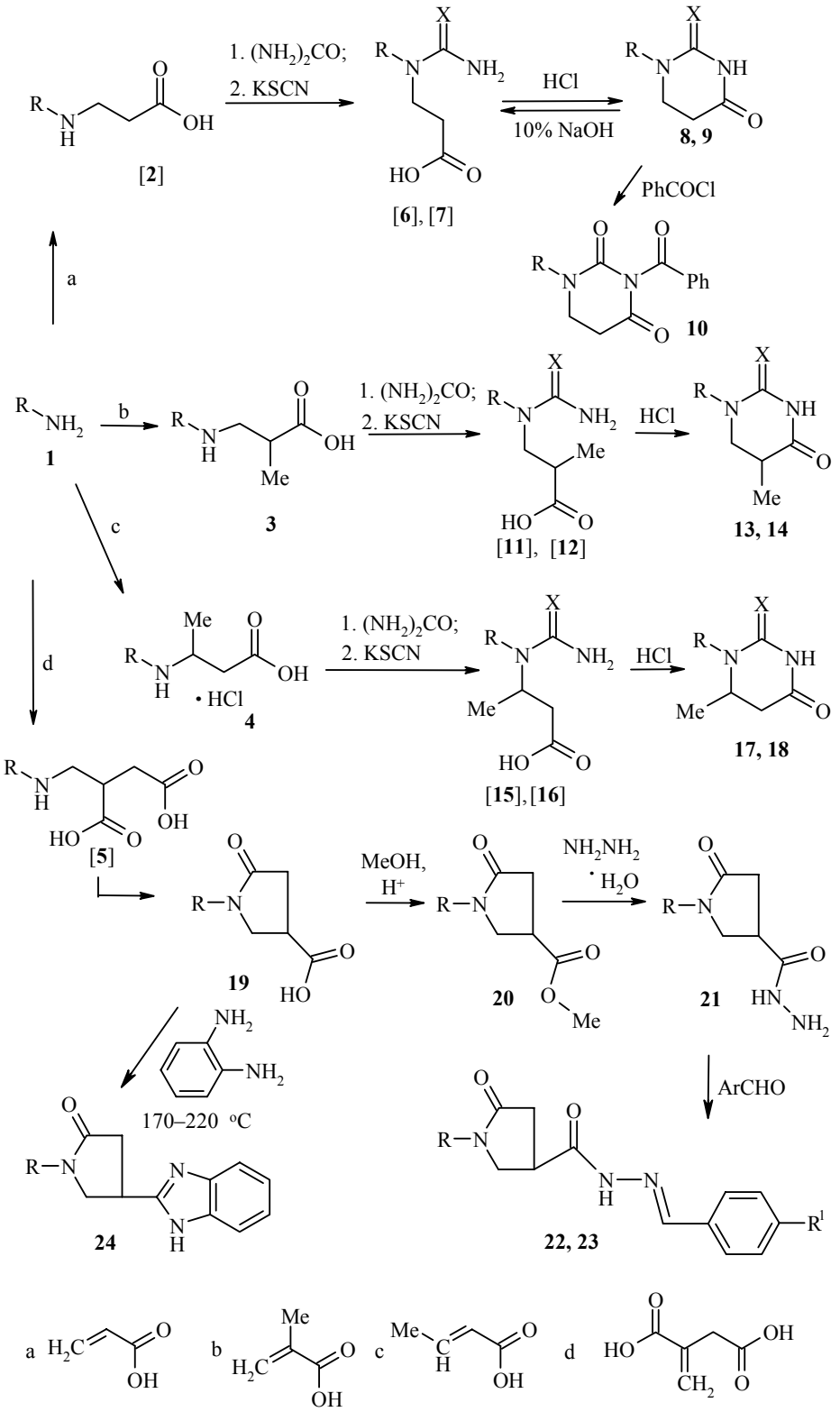

R = 4-PhOC$_6$H$_4$; **22** R^1 = H; **23** R^1 = OMe;
6, **8**, **11**, **13**, **15**, **17** X = O, **7**, **9**, **12**, **14**, **16**, **18** X = S

TABLE 1. Characteristics and Elemental Analysis Data for the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %			mp, °C (solvent)	^{1}H NMR spectrum, δ, ppm (*J*, Hz)*	Yield, %
		C	H	N			
1	2	3	4	5	6	7	8
3	$C_{16}H_{17}NO_3$	71.01 / 70.83	5.97 / 6.32	5.03 / 5.16	100.5-102 (ethanol)	1.15 (3H, d, *J* = 8.2, CH_3); 2.4-2.8 (1H, m, CH); 2.9-3.5 (2H, m, CH_2); 6.5-7.5 (9H, m, arom. H)	54
4	$C_{16}H_{17}NO_3 \cdot HCl$	62.71 / 62.35	5.36 / 5.52	4.38 / 4.55	195.5-197.5 (acetic acid)	1.33 (3H, d, *J* = 8.3, CH_3); 2.4-3.1 (2H, m, CH_2); 3.6-4.1 (1H, m, CH); 6.9-7.8 (9H, m, arom. H); 9.65 (2H, br. s, NH_2^+)	48
6	$C_{16}H_{16}N_2O_4$	64.15 / 63.99	4.98 / 5.37	9.12 / 9.33	152.5-154.5 (ethanol)	2.45 (2H, t, *J* = 7.0, CH_2CO); 3.75 (2H, t, *J* = 7.0, N–CH_2); 5.62 (2H, s, NH_2); 6.9-7.8 (9H, m, arom. H); 11.8–12.6 (1H, br. s, OH)	85
7	$C_{16}H_{16}N_2O_3S$	61.06 / 60.74	4.85 / 5.10	8.68 / 8.85	136.5-138.5 (ethanol)	2.55 (2H, t, *J* = 7.0, CH_2CO); 4.25 (2H, t, *J* = 7.0, N–CH_2); 5.60 (1H, s, NH_2); 6.9-7.6 (9H, m, arom. H)	91
8	$C_{16}H_{14}N_2O_3$	68.31 / 68.08	5.39 / 5.00	9.77 / 9.92	189-191 (ethanol)	2.68 (2H, t, *J* = 6.9, 5-H); 3.72 (2H, t, *J* = 6.9, 6-H); 6.8-7.6 (9H, m, arom. H); 10.39 (1H, s, NH)	44
9	$C_{16}H_{14}N_2O_2S$	64.21 / 64.41	4.93 / 4.73	9.55 / 9.39	190-192 (ethanol)	2.80 (2H, t, *J* = 7.0, 5-H); 3.88 (2H, t, *J* = 7.0, 6-H); 6.9-7.7 (9H, m, arom. H); 11.21 (1H, s, NH)	55
10	$C_{23}H_{18}N_2O_4$	71.88 / 71.49	5.01 / 4.70	7.11 / 7.25	172.5-174 (ethanol)	3.10 (2H, t, *J* = 7.0, 5-H); 4.11 (2H, t, *J* = 7.0, 6-H); 6.9-8.2 (14H, m, arom. H)	90

TABLE 1 (continued)

1	2	3	4	5	6	7	8
13	$C_{17}H_{16}N_2O_3$	68.75 68.91	5.57 5.44	9.28 9.45	201.5-203 (ethanol)	1.12 (3H, d, *J* = 8.2, CH_3); 2.7-3.1 (1H, m, X-portion of AMX, 5-H); 3.5-3.9 (2H, m, AM-portion of AMX, 6-H); 6.9-7.6 (9H, m, arom. H); 10.31 (1H, s, NH)	53
14	$C_{17}H_{16}N_2O_2S$	65.62 65.36	4.98 5.16	8.76 8.97	158.5-160.5 (ethanol)	1.12 (3H, d, *J* = 8.2, CH_3); 2.8-3.2 (1H, m, X-portion of AMX, 5-H); 3.5-4.1 (2H, m, AM-portion of AMX, 6-H); 6.9-7.6 (9H, m, arom. H); 11.22 (1H, s, NH)	67
17	$C_{17}H_{16}N_2O_3$	69.10 68.91	5.31 5.44	9.22 9.45	169.5-171.5 (ethanol)	1.14 (3H, d, *J* = 8.3, CH_3); 2.3-3.3 (2H, m, AM-portion of AMX, 5-H); 3.9-4.2 (1H, m, X-portion of AMX, 6-H); 6.8-7.6 (9H, m, arom. H); 10.38 (1H, s, NH)	55
18	$C_{17}H_{16}N_2O_2S$	65.49 65.36	5.48 5.16	8.76 8.97	156-157.5 (ethanol)	1.21 (3H, d, *J* = 8.0, CH_3); 2.3-3.5 (2H, m, AM-portion of AMX, 5-H); 3.9-4.3 (1H, m, X-portion of AMX, 6-H); 6.9-7.6 (9H, m, arom. H); 11.28 (1H, s, NH)	56
19	$C_{17}H_{15}NO_4$	68.84 68.68	4.85 5.09	4.59 4.71	181-183 (ethanol)	2.6-3.0 (2H, m, 3-H); 3.2-3.5 (1H, m, CH); 3.9-4.2 (2H, m, 5-H); 6.9-7.8 (9H, m, arom. H)	79
20	$C_{18}H_{17}NO_4$	69.18 69.44	5.67 5.50	4.38 4.50	76.5-77.5 (ethanol)	2.6-2.9 (2H, m, 3-H); 3.2-3.6 (1H, m, CH); 3.72 (3H, s, CH_3); 3.8-4.2 (2H, m, 5-H); 6.9-7.8 (9H, m, arom. H)	74
21	$C_{17}H_{17}N_3O_3$	65.76 65.58	5.41 5.50	13.66 13.50	169-171 (dioxane)	2.6-2.8 (2H, m, 3-H); 2.9-3.4 (1H, m, CH); 3.6-4.1 (2H, m, 5-H); 4.33 (2H, br. s, NH_2); 6.8-7.9 (9H, m, arom. H); 9.26 (1H, s, NH)	91
22	$C_{24}H_{21}N_3O_3$	71.95 72.17	5.51 5.30	10.34 10.52	126.5-128 (dioxane)	Mixture of *Z/E*-isomers (60/40); 2.6-3.0 (2H, m, 3-H); 3.2-3.5 (1H, m, CH); 3.8-4.3 (2H, m, 5-H); 6.9-8.4 (14H, m, arom. H); 11.50 and 11.59 (1H, 2s, NH)	84
23	$C_{25}H_{23}N_3O_4$	70.31 69.92	5.29 5.40	9.91 9.78	180-182 (dioxane)	Mixture of *Z/E*-isomers (60/40); 2.6-3.0 (2H, m, 3-H); 3.1-3.5 (1H, m, CH); 3.83 (3H, s, OCH_3); 3.9-4.3 (2H, m, 5-H); 6.8-8.3 (14H, m, arom. H); 11.45 and 11.59 (1H, 2s, NH)	87
24	$C_{23}H_{19}N_3O_2$	74.69 74.78	5.12 5.18	11.31 11.37	171-173 (toluene)	2.8-3.2 (2H, m, 3-H); 3.8-4.1 (1H, m, 4-CH); 4.1-4.4 (2H, m, 5-H); 6.8-8.3 (13H, m, arom. H); 12.93 (1H, s, NH)	44

* ^{1}H NMR spectra were obtained in DMSO-d_6 solutions.

1-Substituted dihydropyrimidinediones are not acylated by acid anhydrides, but are readily acylated by acid chlorides. When 1-(4-phenoxyphenyl)-2,4-(1H,3H)-dihydropyrimidinedione (**8**) is heated with benzoyl chloride in pyridine, the corresponding 3-benzoyl derivative **10** is isolated and in its ^{1}H NMR spectrum we do not see any signal from an amide proton. In the ^{1}H NMR spectrum of the starting compound **8**, the amide proton gives a signal at 10.39 ppm.

In studying the reaction of 4-aminodiphenyl ester (**1**) with itaconic acid, as in [3, 5, 6], we could not isolate the addition product 3-carboxy-N-(4-phenoxyphenylamino)butanoic acid (**5**), since the addition product **5** already formed during the reaction undergoes ring closure to form the derivative of 4-carboxy-2-pyrrolidinone **19**. We studied some chemical conversions of 4-carboxy-1-(4-phenoxyphenyl)-2-pyrrolidinone (**19**).

By treatment with methanol in the presence of sulfuric acid, we obtained the corresponding methyl ester **20**, which then was converted to hydrazide **21** by hydrazinolysis. The carboxylic acid hydrazide **21** is readily condensed with aromatic aldehydes, forming arylidene hydrazides **22, 23**. We obtained the benzimidazole derivative **24** by fusion of compound **19** with *o*-phenylenediamine at 170-220°C.

From the ^{1}H NMR spectra, we see that the arylidene hydrazides **22, 23** in DMSO-d_6 solution exist in the form of two isomers, and give two sets of signals of different intensities. The ratio of *Z/E*-isomers is calculated based on splitting of the signal from the proton of the amide group and is approximately 60/40 for both compounds.

EXPERIMENTAL

The ^{1}H NMR spectra were obtained on a Joel FX 100 (100 MHz) spectrometer, internal standard HMDS. The course of the reactions and the purity of the compounds obtained were monitored by TLC on Silufol UV-254 plates, visualization was carried out in UV light or with iodine vapors.

N-(4-Benzoxyphenyl)-α-methyl-β-alanine (3). 4-Aminodiphenyl ester (**1**) (37.0 g, 0.2 mol), methacrylic acid (25.8 g, 0.3 mol), hydroquinone (1 g), and 50% acetic acid (70 ml) were heated for 15 h at 70°C, then water (150 ml) was added and the precipitated mass was separated by decanting the solvent and washed three times with water. The residue was dissolved in a 10% NaOH solution (200 ml); the unreacted amine was filtered out and the filtrate was acidified with acetic acid down to pH 6. The precipitated oily mass was crystallized out on standing at 5°C. The crystals of compound **3** were filtered out, washed with water, and crystallized from ethanol.

N-(4-Benzoxyphenyl)-β-methyl-β-alanine Hydrochloride (4) was obtained from 4-aminodiphenyl ester (**1**) (37.0 g, 0.2 mol) and crotonic acid (25.8 g, 0.3 mol) by the procedure for synthesis of compound **3**, except the reaction was carried out with boiling. The precipitated oily material, β-alanine **4**, was dissolved in ethyl ether (200 ml), the ether solution was dried by freezing at -20°C and then filtered, and a stream of dry HCl was passed through the ether solution to the saturation point. The precipitated β-alanine hydrochloride **4** was filtered out and washed with acetone and then ether.

N-Carbamoyl-N-(4-phenoxyphenyl)-β-alanine (6). Dihydropyrimidinedione **8** (2.82 g, 0.01 mol) was heated in 10% NaOH (40 ml) to boiling. The mixture was allowed to stand for 30 min at 20°C and filtered. The filtrate was acidified with 20% acetic acid to pH 6. The precipitated crystals of compound **6** were filtered out and washed with water.

N-Thiocarbamoyl-N-(4-phenoxyphenyl)-β-alanine (7) was obtained from the corresponding dihydropyrimidinone-2-thione **9** (2.98 g, 0.01 mol)**,** as for compound **6**.

1-(4-Phenoxyphenyl)dihydro-2,4-(1H,3H)-pyrimidinedione (8). Compound **1** (37.5 g, 0.2 mol), acrylic acid (21.6 g, 0.3 mol), and 50% acetic acid (70 ml) were boiled for 5 h, then water (150 ml) was added and the precipitated mass was separated by decanting the solvent and then was washed three times with water. The residue was dissolved in a 10% NaOH solution (200 ml), the unreacted amine was filtered out, and the filtrate was acidified with acetic acid to pH 6. The precipitated oily mass was dissolved in glacial acetic acid

(100 ml), urea (24 g, 0.4 mol) was added, and the mixture was boiled for 14 h. Conc. HCl (50 ml) was carefully added to the boiling mixture and it was boiled for another 20 min, then water (150 ml) was added. The crystals that precipitated upon cooling were filtered out and washed with water. In order to remove N-substituted ureas, the crystals were dissolved with heating in a 10% sodium hydroxide solution (150 ml), cooled down, and filtered. The filtrate was heated to boiling, acetic acid (35 ml) was carefully poured in, and then conc. HCl was added to pH 0-1 and it was boiled for 10 min. The crystals of dihydropyrimidinedione **8** that precipitated upon cooling were filtered out and washed with water.

1-(4-(Phenoxyphenyl)dihydro-4-(1H,3H)-pyrimidinone-2-thione (9) was obtained as for compound **8**, except that potassium thiocyanate (29.1 g, 0.3 mol) was used instead of urea.

3-Benzoyl-1-(4-phenoxyphenyl)dihydro-2,4-(1H,3H)-pyrimidinone (10). Dihydropyrimidinedione **8** (2.82 g, 0.01 mol), benzoyl chloride (2.08 g, 0.02 mol) in pyrimidine (10 ml) were boiled for 2 h, the mixture was diluted with water (1:10), the precipitated mass was removed, washed three times with water, and crystallized from ethanol.

5-Methyl(or 6-methyl)-1-(4-phenoxyphenyl)dihydro-2,4-(1H,3H)-pyrimidinediones (13, 17). The corresponding β-alanine or its hydrochloride **3, 4** (0.05 mol), urea (6.0 g, 0.01 mol), and acetic acid (25 ml) were boiled for 14 h; conc. HCl (15 ml) was added, and it was boiled for another 15 min. Then the mixture was diluted with water (50 ml) and cooled down; the precipitated crystals of dihydropyrimidinediones **13, 17** were filtered out and washed with water. In order to remove the N-substituted ureas, the crystals were dissolved with heating in a 10% sodium hydroxide solution (30 ml), cooled down, and filtered. The filtrate was heated to boiling, acetic acid (15 ml) was carefully poured in, and then conc. HCl (15 ml) was added and it was boiled for 5-10 min. The crystals of dihydropyrimidinediones **13, 17** that precipitated upon cooling were filtered out and washed with water.

5-Methyl(or 6-methyl)-1-(4-phenoxyphenyl)-4-(1H,3H)-dihydropyrimidinedione-2-thiones (14, 18) were obtained from the corresponding β-alanine or its hydrochloride **3, 4** (0.05 mol) and potassium thiocyanate (5.8 g, 0.06 mol), as for compounds **13, 17.**

4-Carboxy-1-(4-phenoxyphenyl)-2-pyrrolidinone (19). Compound **1** (37.0 g, 0.2 mol) and itaconic acid (32.5 g, 0.25 mol) in 50% acetic acid (250 ml) were boiled for 5 h, the mixture was diluted with water (250 ml) and cooled down, the precipitated crystals were filtered out and washed with water. They were purified twice by dissolving the crystals obtained in 50% NaOH (250 ml), filtering out the unreacted amine, and acidifying the filtrate with 10% HCl to pH 1.

4-Methoxycarbonyl-1-(4-phenoxyphenyl)-2-pyrrolidinone (20). A mixture of 4-carboxy-2-pyrrolidinone **19** (8.91 g, 0.03 mol), methanol (150 ml), and conc. H_2SO_4 (1 ml) was boiled for 8 h. The liquid fractions were distilled off under vacuum. A 5% Na_2CO_3 solution (150 ml) was added to the residue and the mixture was heated to boiling. The crystals of compound **20** that precipitated after cooling were filtered out, washed with water, and crystallized from ethanol.

Hydrazide of 4-Carboxy-1-(4-phenoxyphenyl)-2-pyrrolidinone (21). The methyl ester **20** (6.22 g, 0.02 mol) in a mixture of hydrazine hydrate (4.0 g, 0.08 mol) and 2-propanol (50 ml) was boiled for 30 min. The crystals of hydrazide **21** that precipitated upon cooling were filtered out and washed with 2-propanol and then ether.

Arylidene Hydrazides of 4-Carboxy-1-(4-phenoxyphenyl)-2-pyrrolidinone (22, 23). Hydrazide **21** (1.55 g, 0.005 mol) and the corresponding aldehyde (0.01 mol) were boiled for 2 h in 2-propanol (30 ml) and then cooled down. The precipitated crystals were filtered out and washed with 2-propanol and then ether.

2-{[2-Oxo-4-pyrrolidinyl-1-(4-phenoxyphenyl)]}benzimidazole (24). A mixture of 4-carboxy-2-pyrrolidinone **19** (1.94 g, 0.05 mol) and *o*-phenylenediamine (0.76 g, 0.07 mol) was heated for 3 h at 170°C. Then the temperature was raised to 210-220°C, and heating was continued for another 30 min. A 5% NaOH solution (50 ml) was added to the remaining reaction mass; this was boiled for 5 min and allowed to stand at 20°C for 30 min. The dark-brown crystals formed were filtered out, washed with water, dried, and crystallized from toluene.

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