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Synthesis of Chromophoric Bis-azocrowndilactams

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ABSTRACT

The coupling of 1,2-bis(o-hydroxybenzamido)ethane **1** *with two equivalents of the appropriate arenediazonium chloride in aqueous sodium hydroxide afforded the corresponding 1,2-bis(2-hydroxy-5-arylazobenzoylamino)ethanes* **4–6**. *The latter were converted to the corresponding dipotassium salts* **7–9**, *which were reacted with the appropriate dihalo compound or ditosylate in boiling DMF to give the corresponding 14-17-membered macrocyclic bis-azocrowndilactams* **10–18** *in 58–65% yields. Compound* **14** *was N-alkylated to give the corresponding N,N'-dibenzyl derivative* **19**.

Macrocyclic crown lactams have been the subject of numerous publications and reviews [1]. They are the precursors of azacrown ethers, which have many applications in catalysis [2,3], chromatographic separation of metal cations [4], molecular recognition [5], and biology [6–8]. Moreover, we recently reported the useful applications of some crown lactams in lithium [9,10] and potassium ion selective electrodes [11]. Different methods were reported for the synthesis of these crown lactams [1,12]. Recently, we reported an easy high yield synthesis of crown dilactams [13,14].

The present investigation describes the synthesis of 14-17-membered macrocyclic crown dilactams **10–18** with bis-azo groups suitably located in the molecule to act as potential chromophores useful for spectrophotometric applications.

The synthetic route followed for the synthesis of these macrocycles **10–18** is outlined in Scheme 1. Thus, coupling of 1,2-bis(o-hydroxybenzamido)-ethane **1** in aqueous sodium hydroxide with two equivalents of the appropriate arenediazonium chloride afforded the corresponding 1,2-bis(2-hydroxy-5-arylazobenzoylamino)ethanes **4–6**. The structures of the latter were established by the ^{1}H NMR signal pattern of H-3, H-4, and H-6 of these compounds (cf. Table 1). Thus, for example, compound **5** showed ^{1}H NMR signals for H-3 as a doublet at δ 7.1 (J = 8.8 Hz, ortho coupling), H-4 as a doublet of doublets at 7.95 (J = 8.8 Hz, ortho coupling, J = 2.4 Hz, meta coupling), and H-6 as a doublet at 8.49 (J = 2.4 Hz, meta coupling). The possible formation of the other isomeric bis-azo derivatives **2** and **3** was thus excluded.

The bis-azo compounds **4–6** were converted to their dipotassium salts **7–9** upon treatment with ethanolic potassium hydroxide solution. Treatment of **7–9** with the appropriate dihalo compound or ditosylate in boiling DMF afforded the corresponding macrocycles **10–18** in 58–65% yields. It is noticeable that this reaction proceeds in a short time, affording a high yield of the macrocycles. This averts the high dilution techniques reported for the synthesis of many crown lactams [1,15]. The present findings are comparable to our recently reported synthesis of similar systems where reasonable explanations were given [13,14]. The structures proposed for these macrocycles are consistent with data obtained from ^{1}H NMR spectroscopy, MS, and elemental analyses.

Dedicated to Prof. Dr. Shigeru Oae on the occasion of his seventy-fifth birthday.

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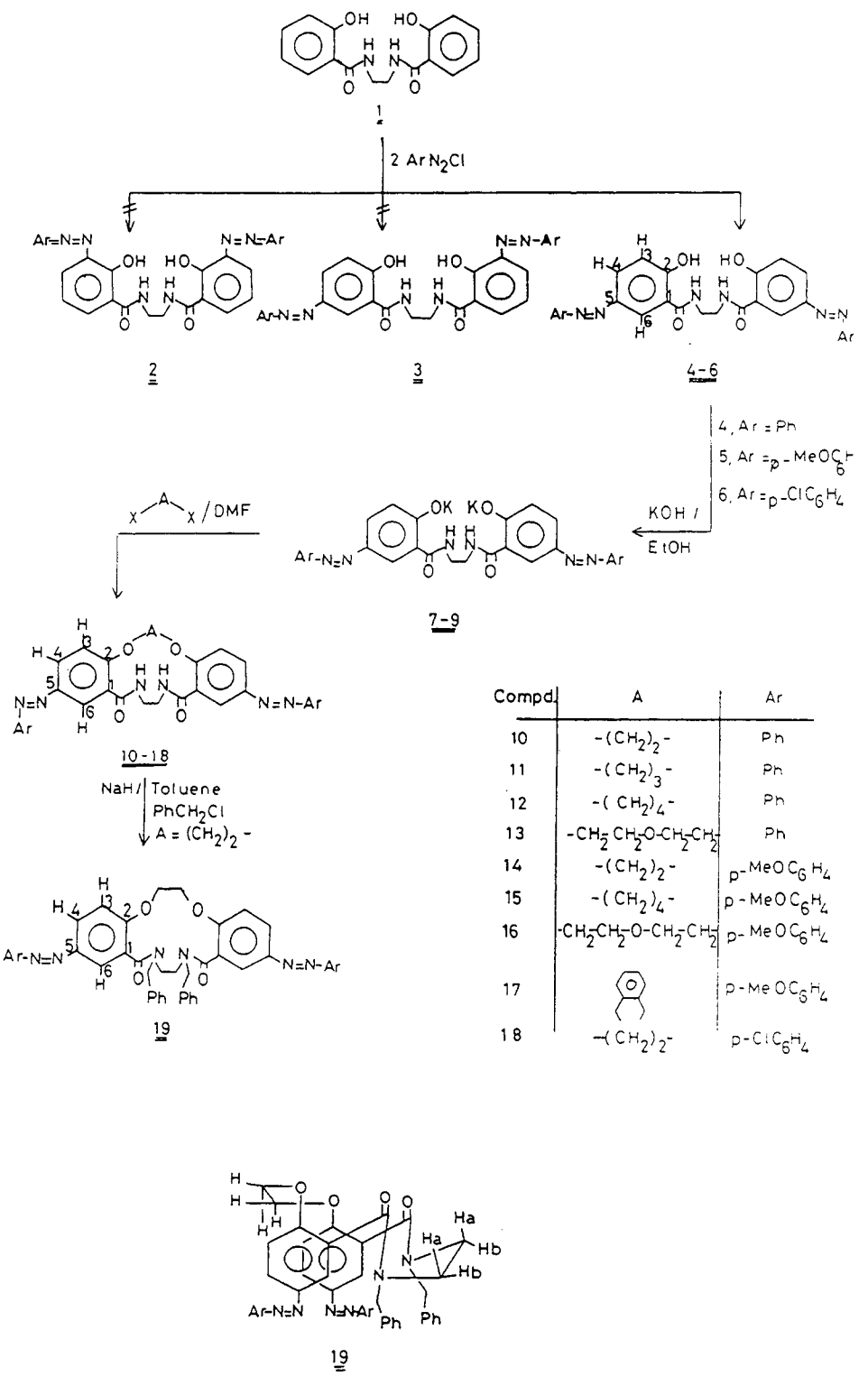
SCHEME 1



Compd.	A	Ar
10	$-(CH_2)_2-$	Ph
11	$-(CH_2)_3-$	Ph
12	$-(CH_2)_4-$	Ph
13	$-CH_2CH_2O-CH_2CH_2-$	Ph
14	$-(CH_2)_2-$	p-$MeOC_6H_4$
15	$-(CH_2)_4-$	p-$MeOC_6H_4$
16	$-CH_2CH_2O-CH_2CH_2-$	p-$MeOC_6H_4$
17		p-$MeOC_6H_4$
18	$-(CH_2)_2-$	p-ClC_6H_4

19

Compound **14** was readily alkylated to the corresponding *N,N'*-dibenzyl derivative **19**. ^{1}H NMR spectra of the latter indicate its existence in the stable trans, trans conformer adopted for similar *N*-alkylated cyclic dilactams and dithiolactams [13,16]. Thus, whereas all NH macrocycles **10–18** showed the equivalence of all OCH_2 and NCH_2 protons in the ^{1}H NMR spectra, compound **19** showed the NCH_2CH_2N at δ 2.88 (d, 2H, J = 9 Hz), 4.82 (d, 2H, J = 9 Hz) beside OCH_2 and NCH_2Ph as overlapped multiplets at 4.38–4.68 (8H), and ArH's at 7.12–7.99 (m, 24H).

TABLE 1 ^{1}H NMR (DMSO-d_6) of Compounds **4–6** and **10–18** (δ)[a]

Compound	NCH_2 (4H)	OCH_2 (4H)	ArH's	NH (2H)	Other Protons
4	3.6 (br s)		7.1–8.56 (m, 16H)	9.3 (br s)	13.3 (OH) (br s)
5	3.6 (br s)		7.07–8.49 (m, 14H)	9.3 (br s)	13.3 (OH), 3.9 (OCH_3) (br s) (s, 6H)
6	3.6 (br s)		7.1–8.55 (m, 14H)	9.26 (br s)	13.2 (OH) (br s)
10	3.58 (br s)	4.7 (s)	7.57–8.28 (m, 16H)	8.54 (br s)	
11	3.6 (br s)	4.35 (m)	7.4–8.4 (m, 16H)	8.47 (br s)	2.1 ($\underline{CH_2}CH_2O$) (m, 2H)
12	3.62 (br, s)	4.7 (m)	7.4–8.05 (m, 16H)	8.4 (br s)	2.12 ($\underline{CH_2}CH_2O$) (m, 4H)
13	3.6 (br s)	4.41 (br s)	7.36–8.37 (m, 16H)	8.43 (br s)	4.0 (CH_2OCH_2) (br s, 4H)
14	3.55 (br s)	4.7 (s)	7.1–8.3 (m, 14H)	8.53 (br s)	3.9 (OCH_3) (s)
15	3.6 (m)	4.3 (t)	7.14–8.34 (m, 14H)	8.4 (br s)	2.1 (CH_2CH_2), 3.88 (OCH_3) (m, 4H) (s, 6H)
16	3.58 (m)	4.4 (m)	7.1–8.35 (m, 14H)	8.42 (br s)	3.78 (OCH_3), 4.0 (CH_2OCH_2) (s, 6H) (m, 4H)
17	3.3 (s)	5.52 (s)	7.14–8.19 (m, 18H)	8.31 (br s)	3.85 (OCH_3) (s, 6H)
18	3.6 (s)	4.75 (s)	7.56–8.28 (m, 14H)	8.52 (br s)	

[a]Some expected signal splitting does not appear to be due to the difficult solubility of these compounds in NMR solvents.
Compound **4** H-3 appears at 7.1 (d, J_{ortho} = 9 Hz), H-4 at 8.0 (dd, J_{ortho} = 9 Hz, J_{meta} = 2 Hz), H-6 at 8.55 (d, J_{meta} = 2 Hz).
Compound **6** H-3 appears at 7.1 (d, J_{ortho} = 9 Hz), H-4 at 8.0 (dd, J_{ortho} = 9 Hz, J_{meta} = 2.2 Hz), H-6 at 8.55 (d, J_{meta} = 2.2 Hz).

The new chromophoric crown lactams **10–19** showed promising cation binding properties in a preliminary spectrophotometric study and could be used for selective microdetermination of some metal cations, especially lithium, sodium, and potassium ions. This study is still underway and will be published separately due to the large quantity of analytical data accumulated.

EXPERIMENTAL

All melting points are uncorrected. NMR spectra were measured on a Varian GEMINI 200 instrument (200 MHz, ^{1}H NMR). Mass spectra were measured (70 eV) on a GCMS-QP 1000 EX spectrometer. Compound **1** was prepared as reported previously [13].

1,2-Bis(2-hydroxy-5-arylazobenzoylamino)ethanes **4–6**

A solution of the appropriate aromatic amine (10 mmol) in water (5 mL) and concd HCl (3 mL) was diazotized at −5°C with a solution of sodium nitrite (0.7 g in 5 mL of water) during 10 minutes. This diazonium salt was then added dropwise with stirring over a period of 30 minutes to a cold (−5°C) solution of **1** (1.5 g, 5 mmol) in aqueous NaOH (20 mL, 30%). After the mixture had been kept overnight in the freezer, acidification with HCl (3N) afforded the crude products **4–6** as yellow precipitates, which were collected and recrystallized from DMF as yellow crystals (Table 2).

Preparation of the Potassium Salts **7–9**

A solution of each of the compounds **4–6** (10 mmol) and KOH (1.14 g, 20 mmol) in ethanol (10 mL) was stirred at room temperature for 10 minutes. The solvent was then removed in vacuo, and the remaining solid was triturated with dry ether, collected, and dried. It was then used in the next step without further purification.

Preparation of the Macrocyclic Bis-azocrowndilactams **10–18**

A solution of each of the potassium salts **7–9** (5 mmol) and the appropriate dihalo compound or ditosylate (5 mmol) in DMF (10 mL) was heated under reflux for 5 minutes (during which time potassium halide precipitated when a dihalo compound was used but no precipitate was observed when a ditosylate was used). The solvent was then removed in vacuo, and the remaining materials were washed with water (50 mL) and recrystal-

TABLE 2 Mp, Yield and Analytical Data of Compounds **4–6** and **10–16**

Compound[a]	Mp (°C) (Yield %)	Formula (MW)	Anal. % Calcd/Found C	H	N
4	285–287 (76)	$C_{28}H_{24}N_6O_4$ (508.54)	66.13 65.90	4.75 4.60	16.53 16.40
5	278–290 (80)	$C_{30}H_{28}N_6O_6$ (568.60)	63.37 63.10	4.96 4.70	14.78 14.60
6	283–285 (72)	$C_{28}H_{22}N_6Cl_2O_4$ (577.43)	58.24 58.10	3.84 3.60	14.55 14.30
10	294–296 (58)	$C_{30}H_{26}N_6O_4$ (534.56)	67.40 67.10	4.90 4.60	15.72 15.80
11	285–287 (61)	$C_{31}H_{28}N_6O_4$ (548.58)	67.87 67.70	5.14 5.00	15.32 15.40
12	283–285 (59)	$C_{32}H_{30}N_6O_4$ (562.61)	68.31 68.00	5.37 5.10	14.93 14.60
13	>300 (61)	$C_{32}H_{30}N_6O_5$ (578.63)	66.42 66.30	5.22 5.10	14.52 14.20
14	293–295 (63)	$C_{32}H_{30}N_6O_6$ (594.63)	64.64 64.50	5.08 5.00	14.13 14.20
15	282–284 (62)	$C_{34}H_{34}N_6O_6$ (622.69)	65.58 65.30	5.50 5.40	13.50 13.60
16	>300 (65)	$C_{34}H_{34}N_6O_7$ (638.69)	63.94 63.70	5.37 5.10	13.16 13.30
17	268–270 (58)	$C_{38}H_{34}N_6O_6$ (670.73)	68.05 68.00	5.11 4.90	12.53 12.30
18	>300 (60)	$C_{30}H_{24}N_6Cl_2O_4$ (603.47)	59.71 59.50	4.01 3.90	13.93 13.70
19	272–274 (56)	$C_{46}H_{42}N_6O_6$ (774.88)	71.30 71.10	5.46 5.30	10.84 10.70

[a]Compound **10** MS: m/z = 534 (M^+, 13%). Compound **11** MS: m/z = 548 (M^+, 18%). Compound **12** MS: m/z = 562 (M^+, 19%). Compound **13** MS: m/z = 578 (M^+, 32%). Compound **14** MS: m/z = 594 (M^-, 18%).

lized from DMF to give yellow crystals of compounds **10–18** (Table 2).

3,12-Diphenylazo-5,6,7,8,9,10,16,17-octahydrodibenzo[e,m] [1,4,8,11]-dioxadiazacyclotetradecine-5,5,10-dione **10** was obtained from **7** and 1,2-dibromoethane.

3,12-Diphenylazo-5,6,7,8,9,10,17,18-octahydro-16H-dibenzo[b,j][1,12,5,8]-dioxadiazacyclopentadecine-5,10-dione **11** was obtained from **7** and 1,3-dibromopropane.

2,13-Diphenylazo-6, 7, 8,9,15,16,17,18,19,20-decahydrodibenzo[b,j][1,12,5,8]dioxadiazacyclohexadecine-15,20-dione **12** was obtained from **7** and 1,4-dibromobutane.

2,14-Diphenylazo-6,7,9,10,16,17,18,19,20,21-decahydrodibenzo [h,p][1,4,7,11,14] trioxadiazacycloheptadecine-16,21-dione **13** was obtained from **7** and diethylene glycol ditosylate.

3,12-Di-p-methoxyphenylazo- 5, 6, 7, 8,9,10,16,17-octahydrodibenzo [e,m][1,4,8,11]dioxadiazacyclotetradecine-5,10-dione **14** was obtained from **8** and 1,2-dibromoethane.

2,13-Di-p-methoxyphenylazo- 6, 7, 8,9,15,16,17, 18,19,20-decahydrodibenzo[b,j][1,12,5,8]dioxadiazacyclohexadecine-15,20-dione **15** was obtained from **8** and 1,4-dibromobutane.

9,18-Di-p-methoxyphenylazo-5, 11,12, 13,14,15, 16,22-octahydrotribenzo [b,j,n] [1,12,5,8] dioxadiazacyclohexadecine-11,16-dione **16** was obtained from **8** and α,α-dibromo-o-xylene.

2,14-Di-p-methoxyphenylazo-6,7,9,10,16,17,18, 19,20,21-decahydrodibenzo [h,p] [1,4,7,11,14]trioxadiazacycloheptadecine-16,21-dione **17** was obtained from **8** and diethylene glycol ditosylate.

3,12-Di-p-chlorophenylazo-5,6,7,8,9,10,16,17-octahydrodibenzo [e,m] [1,4,8,11] dioxadiazatetradecine-5,10-dione **18** was obtained from **9** and 1,2-dibromoethane.

3,12-Di-p-methoxyphenylazo-5,6,7,8,9,10,16,17-octahydro-6,9-dibenzyl-dibenzo [e,m]-[1,4,8,11]dioxadiazacyclotetradecine-5,10-dione **19**

Sodium hydride (0.25 g, 50% suspension in mineral oil, ca. 5 mmol) was washed with pentane and suspended in toluene (10 mL). To this suspension was added a solution of **14** (0.6 g, 1 mmol) in tol-

uene (10 mL) under nitrogen. After the mixture had been stirred for 1 hour at 50°C, a solution of benzyl chloride (0.26 g, 2 mmol) in toluene (2 mL) was added, and the mixture was heated under reflux for 24 hours. The solvent was then removed in vacuo, and the residue was extracted with methylene chloride (50 mL), washed with water (100 mL), and then dried over $MgSO_4$. After filtration and evaporation of the solvent, the remaining solid was recrystallized from DMF/ethanol to give yellow crystals of **19** (Table 2).

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