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New Synthesis of 28- and 30- Crown-Formazans and Bis Formazans

Ashraf A. Abbas

Department of Chemistry, Faculty of Science, Cairo University, Giza, A. R. Egypt

E-mail: aadayam@frcu.eun.eg or ashraf@chem-sci.cairo.eun.eg

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Abstract: The macrocyclic cyano crown formazans **3a-c** and cyano crown formazans with two formazyl moieties **4a-c** were prepared by the azo coupling of the appropriate bis diazonium salts **2a-c** with cyanoacetic acid in different medium. The Bis macrocyclic crown formazan **9** was prepared by condensation of 1,3-diaminopropane with the 16-oxo crown formazan **8**. The latter was prepared by ozonolysis of 16-methylene crown formazan **3a**. © 1998 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

The Chemistry and diverse application of formazans have been the subject of a large number of reviews that have been cited previously.[1] Moreover, there is recent growing interest in the synthesis of macrocyclic crown formazans especially cyano formazans due to their useful application in selective metal extraction[2-5] and determination.[6-15] Such applications depend mainly on the cavity size of the macrocyclic crown formazans as well as on the substituents in the macrocycle. The increase hydrolytic stability of the metal complexes of crown formazans compared with that of azacrown ethers was explained by the presence of a rigid block with one carbon and four nitrogens linked in a cyanine like system incapable of inversion.[16] Thus, for example, compound **I** [R = NO_2, CN, X = $(CH_2)_3$, $CH_2{=}C(CH_2)_2$, $C_6H_4(CH_2)_2(o)$] were used for selective spectrophotometeric determination of lithium.[6,8,17] Also, **I** [CN, X = $(CH_2)_3$] forms a useful cesium ion selective electrode.[11] On the other hand, compounds **I** [R = Ph, CN, X = $C_2H_4(OC_2H_4)n$, n = 0-2] were reported to be useful for selective extraction of Cu and Hg.[3,5] The present study describes new useful approach for the synthesis of a number of cyano crown formazans with two formazyl moieties and bis formazan of expected useful applications.

RESULTS AND DISCUSSIONS

The synthesis of cyano macrocyclic crown formazan **3a** was reported in many publications as the sole product of the reaction between the corresponding bis-diazotized bis(2-aminophenoxy)-1,3-propane **2a** and

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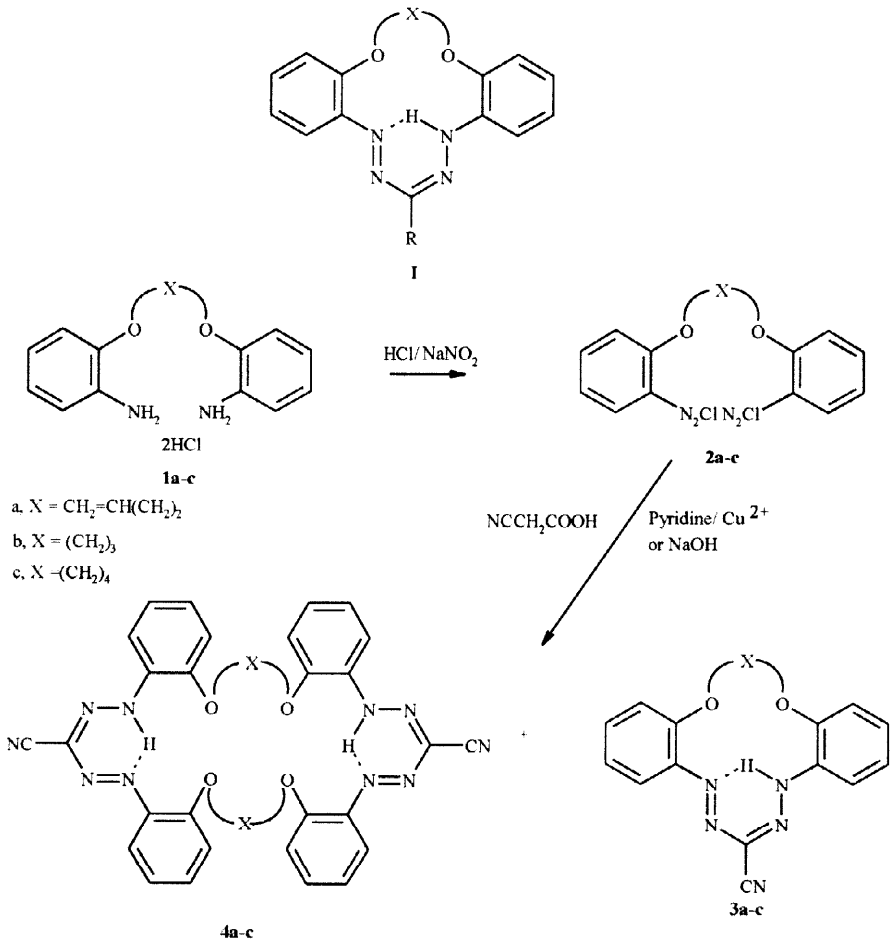
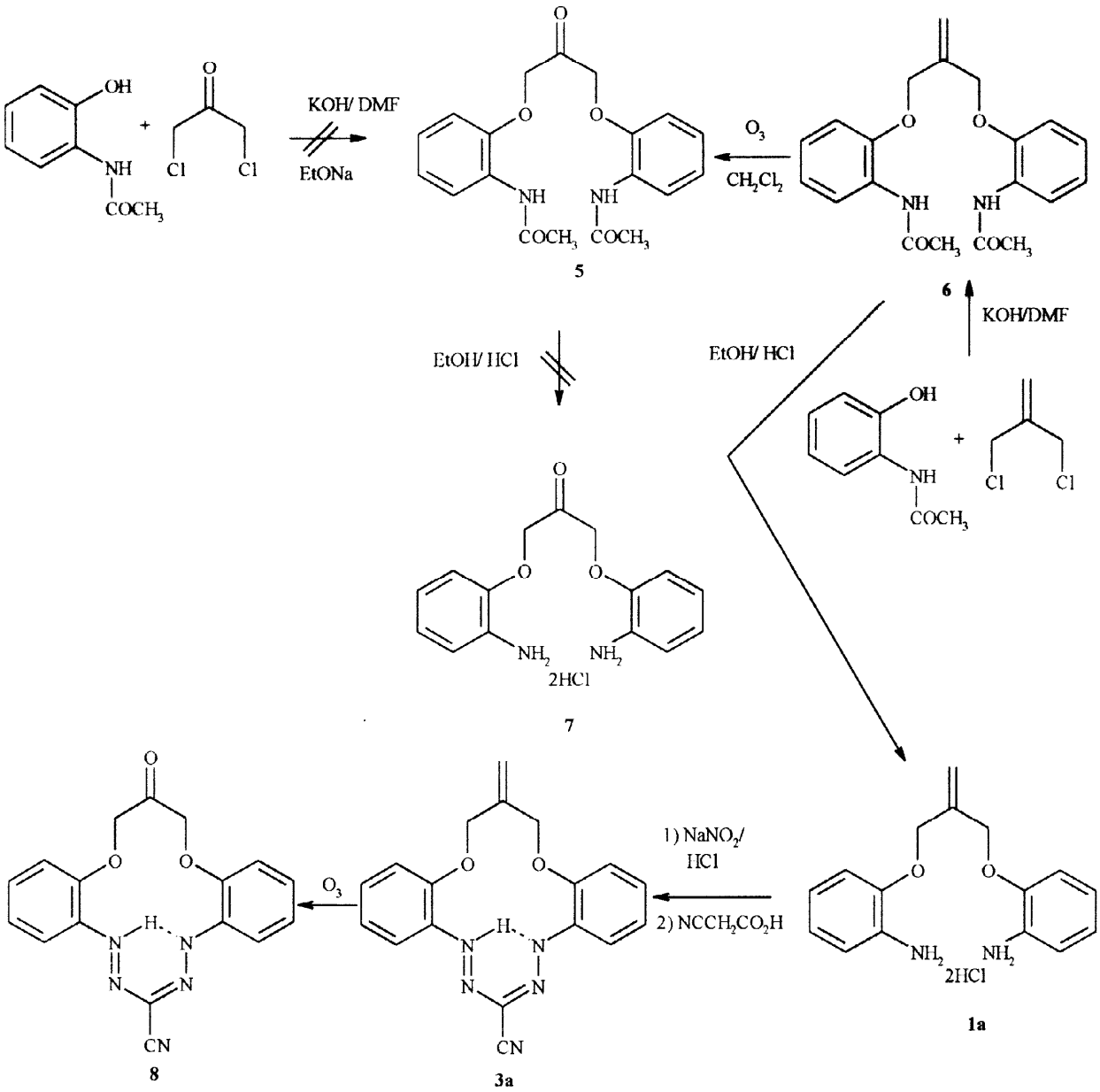
cyanoacetic acid in pyridine containing $CuSO_4$ in 18% yield and the authors failed to separate any other identifiable product from the dark brown reaction mixture.[17]

This paper describes the synthesis of new macrocyclic crown formazan **4a** with two formazyl moieties from the above reaction mixture with some modification. Thus, the bis diamine dihydrochloride **1a** was diazotized with sodium nitrite in hydrochloric acid to give the corresponding bis-diazotized bis(2-aminophenoxy)-1,3-propane **2a** which was coupled with cyanoacetic acid in NaOH or pyridine containing $CuSO_4$ to give in addition to 7-cyano macrocyclic crown formazan **3a** another pure sample of the macrocyclic crown formazan **4a** which contain two formazyl moieties. The structure of the latter was proved by elemental analysis, ^1H NMR and mass spectra. This results stimulated the attention of the author to study the coupling of bis-diazotized bis(2-aminophenoxy)-1,3-propanes **2b**[1],**c**[18] with cyanoacetic acid in different media which afforded the macrocyclic crown 7-cyano formazans **3b,c** and macrocyclic crown formazans **4b,c** as shown in Scheme 1.



Scheme 1

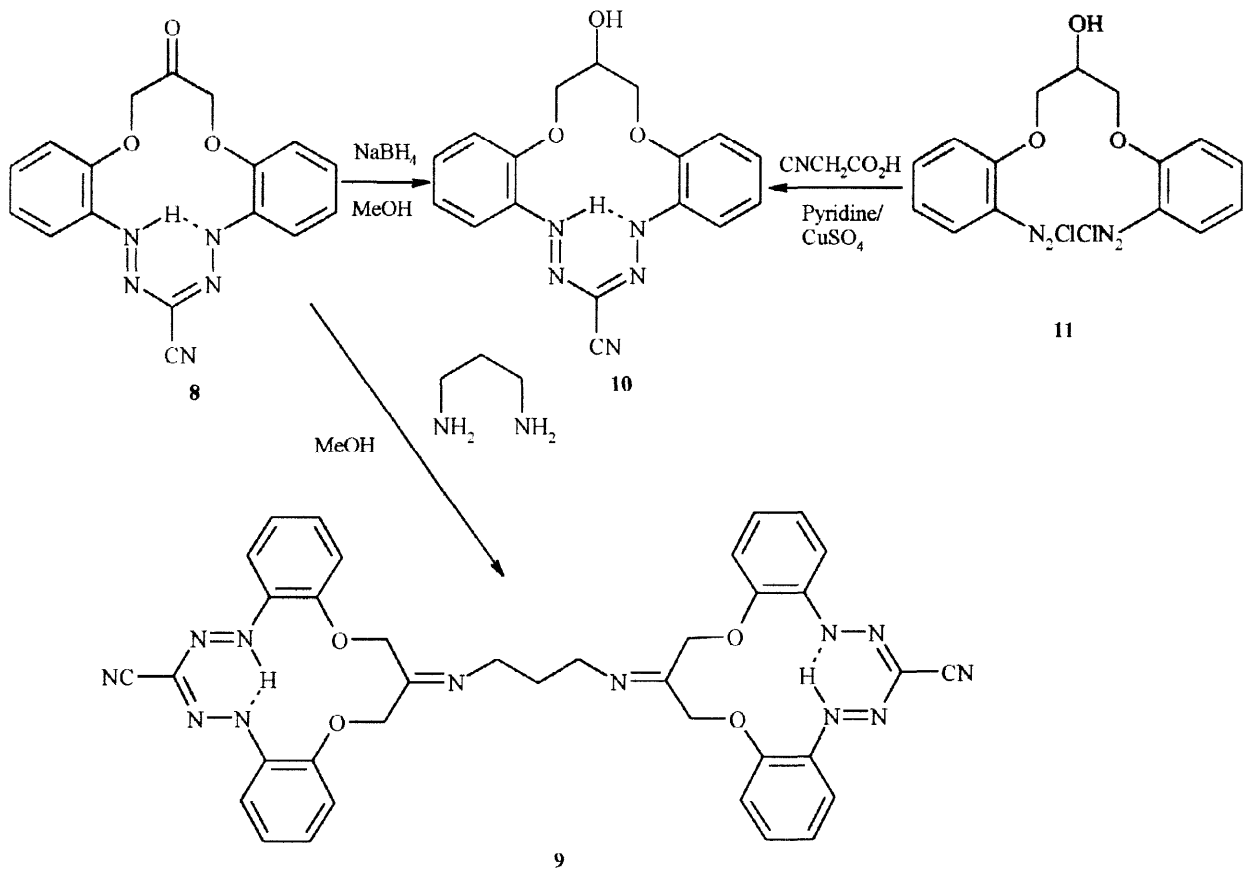
Compounds **4a-c** were separated from **3a-c** by preparative thin layer chromatography (TLC) using suitable eluent for each derivatives. This paper also describes the synthesis of the new macrocyclic crown formazan **8**



Scheme 2

and bis formazan **9** as shown in the Scheme 2 and 3. Thus, reaction of acetamidophenol with 1,3-dichloroacetone in basic medium (KOH/DMF or EtONa or $CsCO_3$/DMF) failed to give the corresponding bis acetamidophenol derivatives **5** and instead a polymeric product was obtained from the reaction mixture (propably polymeric aldol condensation products were formed). The bis acetamidophenol derivatives **5** was only obtained by ozonolysis of the corresponding 2-methylene-1,3-bis(2-acetamidophenoxy)propane (**6**) (which was obtain from the bis alkylation of the potassium salt of acetamidophenol with 2-chloromethyl-3-chloropropene).[1] Attempted hydrolysis of **5** to the corresponding bis amine hydrochloride 7 in ethanolic solution containing conc. hydrochloric acid was also unsuccessful. Compound **8** has been obtained only by

ozonolysis of compound **3a** (which was obtain by coupling of cyanoacetic acid with the diazonium salt of 2-methylene-1,3-bis(aminophenoxy)propane dihydrochoride **1a**[17]) in CH_2Cl_2 at −80 °C. The structure of compound **8** was confirmed by the following facts: i) Reduction of compound **8** in methanolic solution containing $NaBH_4$ gave the corresponding macrocyclic crown formazan **10** which was previously obtained by coupling of the bis diazotized bisamine **11** with cyanoacetic acid[18]; ii) Reaction of compound **8** with the 1,3-diaminopropane in methanolic solution gave the corresponding bis macrocyclic formazan **9**; and iii) Compound **8** gave the correct molecular ion peak in its mass spectra and the characteristic bands for CN and CO groups in its IR spectra.



Scheme 3

EXPERIMENTAL

All melting points are uncorrected. Compounds prepared were characterized by mixed melting points. IR spectra (KBr) were recorded on a Perkin-Elmer 1430 spectrophotometer. NMR spectra were measured with a Varian GEMINI 200 spectrometer (200 MHz ^{1}H NMR). Mass spectra were recorded on a Finigan Mat

312 (70 EV) or a Finigan Mat 1125 (70 EV) spectrometer. Elemental analyses were carried out at the Microanalytical Centre, Cairo University and Univeristat of Konstanz (Germany). 1,3-diaminopropane and 1,3-dichloroacetone, 2-chloromethyl-3-chloropropene were used as purchased from Aldrich.

Synthesis of macrocyclic formazans 3a-c and 4a-c

General procedure A: a solution of the appropriate diamine dihydrochloride **1a-c** (1 mmol) in water (5 ml) and conc. HCl (3 ml) was diazotized at –5°C with a solution of sodium nitrite (0.23 g in 5 ml water) during ½ h. Stirring was continued for 1 h at –5°C and then added dropwise with stirring to a solution containing cyanoacetic acid in water (10 ml) containing NaOH (1.2 g) over a period of 1 h. The reaction mixture was then kept in the freezer overnight. The solid precipitated was collected and purified on preparative TLC using silica gel (60 F_{254}) with proper eluent for each derivative.

General procedure B: a solution of the appropriate diamine dihydrochloride **1a-c** (1 mmol) in water (5 ml) and conc. HCl (3 ml) was diazotized at –5°C with a solution of sodium nitrite (0.23 g in 5 ml water) during ½ h. Stirring was continued for 1 h at –5°C and then added dropwise with stirring to a solution of cyanoacetic acid (1 mmol) in pyridine (150 ml), 0.5 g of $CuSO_4.5H_2O$ and 20 ml water at –5°C over a period of 1 h. The reaction mixture was then kept in the freezer overnight. The solid precipitated by adding conc. HCl was collected and purified on preparative TLC using silica gel (60 F_{254}) with proper eluent for each derivatives.

16-Methylene-16,17-dihydro-5H,15H-dibenzo[b,i][1,11,4,5,7,8]dioxatetraazacyclotetradecine-7-carbonitrile (3a)

1- With the use of the general procedure A **1a** gave 0.03 g (10%) of deep red crystals of **3a** using a mixture of chloroform/ petroleum ether (40-60) 2:1 as an eluent (R_f= 0.63), mp 254°C (lit.[17] mp = 252-255°C)

2- With the use of the general procedure B **1a** gave 0.05 g (15%) of **3a**.

16,17-Dihydro-5H,15H-dibenzo[b,i][1,11,4,5,7,8]dioxatetraazacyclotetradecine-7-carbonitrile (3b)

1- With the use of the general procedure A **1b** gave 0.035 g (11%) of deep red crystals of **3b** using chloroform as an eluent (R_f= 0.73), mp 240-50 °C (lit.[19] mp = 250-251°C)

2- With the use of the general procedure B **1b** give 0.063 g (20%) of **3b**.

5H-15,16,17,18-Tetrahydrodibenzo[b,i][1,14,4,5,7,8]dioxatetraazacyclopentadecine-7-carbonitrile (3c)

1- With the use of the general procedure A **1c** gave 0.03 g (9%) of deep red crystals of **3c** using chloroform as an eluent (R_f = 0.75), mp 209-211°C; IR (cm^{-1}) 2223.8 (CN); Ms:m/z 335 (M^+, 100%), 212 (13.5%), 183(12.2%), 162(16.2%), 91(34%), 77(32%), 65(50%), 55 (77.8%). ^{1}H NMR ($CDCl_3$) δ 2.11 (t, J = 1.5 Hz, 4H, $OCH_2\underline{CH_2}$), 4.11 (t, J = 2.1 Hz, 4H, OCH_2), 6.93-7.(m, 8H, ArH's), 14.69 (s, 1H, NH). (Calcd. for $C_{18}H_{17}N_5O_2$ (335.36): C, 64.47; H, 5.11; N, 20.88. Found: C, 64.31; H, 5.01; N, 20.92)

2- With the use of the general procedure B **1c** gave 0.045 g (15%) of **3c**.

*16,34-Dimethylene-5H,17H,23H,35H-16,17,33,34-tetrahydrotetrabenzo[b,i,p,w]-[1,11,15,25,4,5,7,8,18,19,21,22]tetraoxaoctaazacyclooctacosine-7,25-dicarbonitrile (**4a**).*

1- With the use of the general procedure A **1a** gave 0.046 g (7%) of deep red crystals of **4a** using chloroform as an eluent (R_f = 0.46), mp 240-242°C; IR (cm^{-1}) 2225 (CN); Ms:m/z 667 (M+1, 118%), 338 (11.3%), 214 (40.3%), 177 (14.6%), 145 (49.4%), 108 (100%); ^{1}H NMR (DMSO) δ 4.88 (s, 8H, OCH_2), 5.38 (s, 4H, C=CH_2), 6.89-7.52 (m, 16H, ArH's,), 12.35 (s, 2H, NH). (Calcd. for $C_{36}H_{30}N_{10}O_4$ (666.69): C, 64.86; H, 4.54; N, 21.01. Found: C, 64.70; H, 4.50; N, 20.97).

2- With the use of the general procedure B **1a** gave 0.03 g (5%) of **4a**.

*5H,23H,17H,36H-15,16,33,34-Tetrahydrotetrabenzo[b,i,p,w][1,11,15,25,4,5,7,8,18,19,21,22]-tetraoxaoctaazacyclooctacosine-7,25-dicarbonitrile (**4b**).*

1- With the use of the general procedure A **1b** gave 0.04 g (7%) of deep red crystals of **4b** using chloroform as an eluent (R_f= 0.48), mp 242°C; IR (cm^{-1}) 2229.8 (CN); Ms:m/z 642 (M^+, 7%), 614 (5.6%), 586 (7.6%), 558 (4.4%), 147 (74%), 120 (82%), 77 (85%), 65 (100%), 41 (96%); ^{1}H NMR ($CDCl_3$) δ 2.31 (quintet, J = 6.25 Hz, 4H, OCH_2CH_2), 4.26 (t, J = 6 Hz, 8H, OCH_2), 6.92-7.65 (m, 16H, ArH's,), 13.25 (s, 2H, NH). (Calcd. for $C_{34}H_{30}N_{10}O_4$ (642.67): C, 63.54; H, 4.70; N, 21.79. Found: C, 63.31; H, 4.65; N, 21.48)

2- With the use of the general procedure B **1b** gave 0.03 g (5%) of **4b**.

*5H,24H,-16,17,18,19,35,36,37,38-Octahydrotetrabenzo[b,i,q,x][1,11,16,26,4,5,7,8,19,20,22,23]-tetraoxaoctaazacyclotricontene-7,26-dicarbonitrile (**4c**).*

1- With the use of the general procedure A **1c** gave 0.03 g (5%) of deep red crystals of **4c** using chloroform as an eluent (R_f = 0.17), mp 237-239°C; IR (cm^{-1}) 2218 (CN); Ms:m/z 671 (M^+, 13.1%), 394 (12%), 254 (14%), 198 (18.2%), 160 (48.8%), 150 (15.1%), 115 (25.3%), 77 (58.3%), 52 (100%); ^{1}H NMR ($CDCl_3$) δ 2.16 (t, J = 1.6 Hz, 8H, OCH_2CH_2), 4.32 (t, J = 2.2 Hz, 8H, OCH_2), 6.81-7.43 (m, 16H, ArH's), 10.73 (s, 2H, NH). (Calcd. for $C_{36}H_{34}N_{10}O_4$ (670.72): C, 64.47; H, 5.11; N, 20.88. Found: C, 64.40; H, 5.05; N, 20.79).

2- With the use of the general procedure B **1c** gave 0.04 g (6%) **4c**.

*1,3-Bis(2-acetamidophenoxy)propan-2-one (**5**)*

To a cold stirring solution of **2** (2 g, 5.6 mmol) in methylene chloride at –80°C was passed a steam of ozone for about 1.5 h till a blue color appeared. Then the steam of ozone was stopped and 5.6 mmol of Ph_3P was added to the reaction mixture. The reaction was stirred for about 4 h at –80°C then at room temperature overnight. The solvent was then removed under vacuum. The solid obtained by adding ether was collected, dried and crystallized from toulene to give 1.3 g (65%)of colorless crystals of **2**, mp 136°C; ^{1}H NMR ($CDCl_3$)

δ 2.17 (s, 6H, CH_3CO) 4.88 (s, 4H, OCH_2), 6.73-8.29 (m, 10H, ArH's, NH). (Calcd. for $C_{19}H_{20}N_2O_5$ (356.37): C, 64.04; H, 5.66; N, 7.86. Found: C, 63.94; H, 5.60; N, 7.72).

16-Oxo-16,17-dihydro-5H,15H-dibenzo[b,i][1,11,4,5,7,8]dioxatetraazacyclotetradecine-7-carbonitrile (8)

In a cold stirring solution of **3a** (2 g, 6 mmol) in methylene chloride at –80°C was passed a steam of ozon for about 1.5h till a blue color appeared. Then the steam of ozone was stoped and 6 mmol of Ph_3P was added to the reaction mixture. The reaction was stirred for about 4 h at –80°C then at room temperature overnight. The solvent was then removed under vacuum. The solid obtained was collected, dried and purified on a column chromatography using chloroform as an eluent (R_f= 0.2). The solid obtained after column chromatography was crystallized from methanol to give 1.2 g (60%) of deep red crystals of **8,** mp 228°C; IR (cm^{-1}) 2225.7 (CN), 1703 (CO); Ms:m/z 336 (M+1, 74.4%), 213 (12.3%), 183 (14.7%), 148 (68.6%), 120 (100%), 93 (55.7%), 52 (94%). ^1H NMR (DMSO) δ 5.03 (s, 4H, OCH_2), 7.07-7.87 (m, 8H, ArH's), 15.88 (s, 1H, NH); (Calcd. for $C_{17}H_{13}N_5O_3$ (335.32): C, 60.89; H, 3.91; N, 20.89. Found: C, 60.74; H, 3.82; N, 20.72).

16-Hydroxy-16,17-dihydro-5H,15H-dibenzo[b,i][1,11,4,5,7,8]dioxatetraazacyclotetradecine-7-carbonitrile (10)

To a hot stirred solution of **8** (1 g, 3 mmol) in methanol (20 ml) was added solid $NaBH_4$ (0.11g, 3 mmol) over a period of 10 minutes. The reaction mixture was heated under reflux for 1 h. The solvent was then removed under vacuum and the remaining materials was washed with water. The solid obtained was collected and purified on preparative thin layer chromatography (TLC) using silica gel (60 F_{254}) with chloroform as an eluent (R_f = 0.62) to give 0.65 g (85%) of deep red crystals of **10**, mp 275-277°C [lit[19]. mp = 274°C].

1,3-Bis(16-methyleneimino-16,17-dihydro-5H,15H-dibenzo[b,i][1,11,4,5,7,8]dioxatetraazacyclotetradecine-7-carbonitrile)propane (9)

To a solution of **8** (2 g, 6 mmol) in methanol (20 ml) was added 1,3-diaminopropane (10 mmol) and few drops of glacial acetic acid. The reaction mixture was heated under reflux for 1h. The solvent was then removed under vacuum and the solid obtained was collected by filtration and crystallized from methanol to give 1.5 g (70%) of deep red crystals of **9**, mp 198°C; IR (cm^{-1}) 2219.9 (CN), 1588 (imine C=N); ^1H NMR ($CDCl_3$) δ 1.61 (quintet, J = 2 Hz, 2H, $NCH_2\underline{CH_2}$), 2.29 (t, J = 5.8 Hz, 4H, NCH_2), 4.33 (s, 8H, OCH_2), 7.01-7.92 (m, 16H, ArH's,), 16.05 (s, 2H, NH). (Calcd. for $C_{37}H_{32}N_{12}O_4$ (708.73): C, 62.70; H, 4.55; N, 23.72. Found: C, 62.59; H, 4.50; N, 23.96).

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