Pergamon

Tetrahedron, Vol. 53, No. 9, pp. 3223-3230, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00033-1

Synthesis of Pyrrolo[2,1-*c*][1,4]benzodiazepine Antibiotics: Oxidation of Cyclic Secondary Amine With TPAP

Ahmed Kamal,[1*] Philip W. Howard,[2] B.S. Narayan Reddy,[1] B.S. Praveen Reddy,[1] David E. Thurston[2]

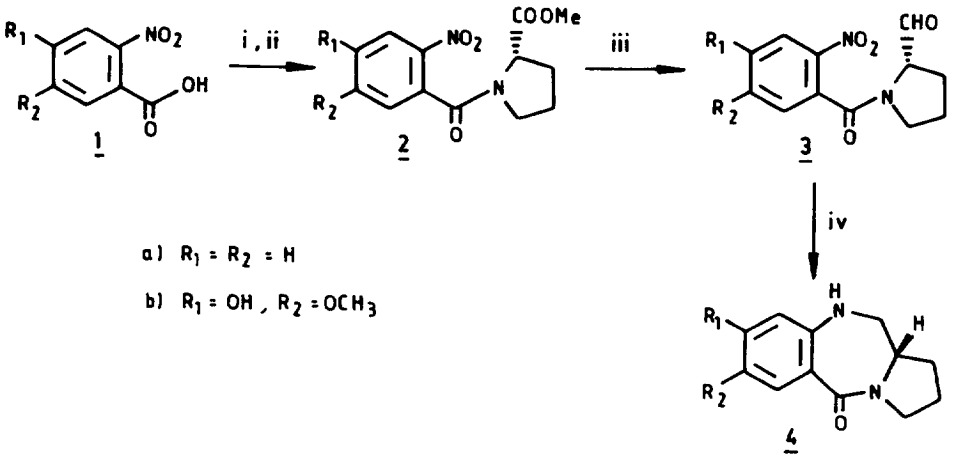
[1]Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500 007, India

[2]School of Pharmacy and Biomedical Sciences, University of Portsmouth, Portsmouth, UK PO1 2DZ

Abstract: A facile procedure for the preparation of the imine form of the pyrrolo[2,1-*c*][1,4]-benzodiazepine ring system by the oxidation of cyclic secondary amine with catalytic amounts of tetra-n-propylammonium perruthenate (TPAP) and N-methylmorpholine N-oxide (NMO) as a co-oxidant is described. This oxidative method is devoid of side-products and is thus a significant improvement over the Swern oxidation previously reported.

The pyrrolo[2,1-*c*][1,4]benzodiazepine (PBD) class of antitumour antibiotics is produced by various *Streptomyces* species; well known members include anthramycin and DC-81.[1] These compounds exert their biological activity by covalently binding to the N-2 of guanine in the minor groove of DNA through the imine or imine equivalent functionality at N10-C11 of the PBD. This aminal linkage thus interferes with DNA function.[2] Furthermore, these molecules have been shown to interact with DNA in a sequence-selective manner and as a result may have potential as therapeutics to inactivate particular genes.[3] Various approaches to the synthesis of these compounds have been investigated over the past few years.[4,5] These methods have met with varying degrees of success and have different limitations.[5] Although PBDs with either a secondary amine or amide functionality at N10-C11 are readily synthesized, the introduction of an imine or carbinolamine at this position has generally given problems because of the reactivity of these functional groups.

In the literature, some procedures have been developed only recently which allow the biologically and synthetically relevant transition-metal catalyzed transformation of amines into imines.[6] In our search for more practical and efficient methodologies, we recently developed a new approach for the PBD imine via the mild oxidation of the secondary amine with activated DMSO.[7] With a view to widen the applicability of this method we became interested in the investigation of other milder oxidation reagents. After the introduction of tetra-n-propylammonium perruthenate (TPAP) as a catalyst[8] for the oxidation of alcohol groups in 1987, it has found extensive applications.[9] Its mildness and chemoselectivity, and commercial availability has made it the reagent of choice in the oxidation of hydroxyl groups in very critical and delicate environments,[10] where other methods often fail. Recently, TPAP has been employed for the conversion of secondary amines to the corresponding imines.[11]

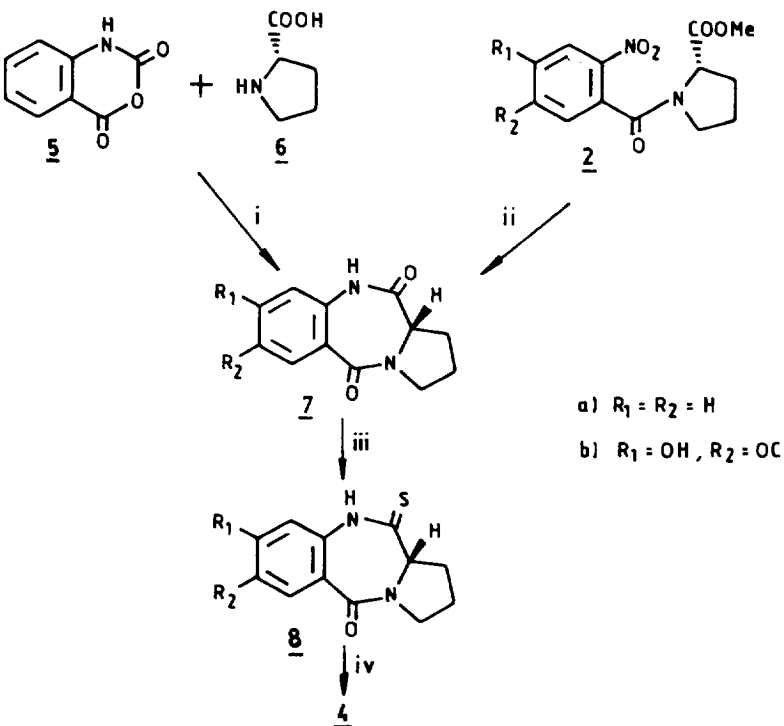


a) $R_1 = R_2 = H$

b) $R_1 = OH$, $R_2 = OCH_3$

i) $SOCl_2$, C_6H_6, RT, 3-4h ii) L-proline methylester hydrochloride, Et_3N, THF, 0°C, 1h
iii) DIBAL-H, CH_2Cl_2, -78°C, 45min. iv) 10% Pd-C, H_2 (1.5atm), 6h

Scheme-1



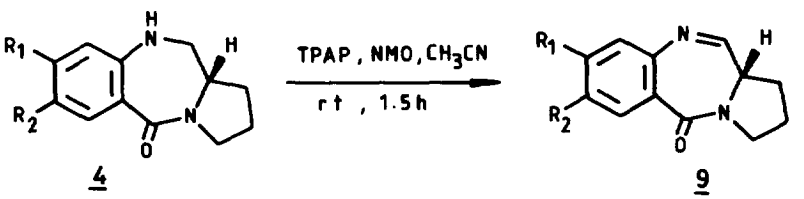
a) $R_1 = R_2 = H$

b) $R_1 = OH$, $R_2 = OCH_3$

i) DMF, Δ, 5h ii) $SnCl_2 \cdot 2H_2O$, MeOH, Δ, 1h iii) [p CH_3O-$C_6H_4PS_2$]$_2$ / Toluene / 70° / 3-4h iv) Raney nickel, EtOH, Δ, 5-6h

Scheme-2

In this paper, we report the use of TPAP for conversion of PBD secondary amine to its imine form. The precursors were synthesized by coupling the appropriate 2-nitrobenzoic acids (**1**) via their acid chlorides with (2S)-proline methylester hydrochloride to afford the methyl(2S)-N-(2-nitrobenzoyl)pyrrolidine-2-carboxylates (**2**), followed by reduction with DIBAL-H to give the (2S)-N-(2-nitrobenzoyl)pyrrolidine-2-carboxaldehydes (**3**). Then reductive cyclization of **3** in the presence of 10% Pd-C provided the cyclic secondary amine precursors **4**. These precursors **4** have also been synthesized by altogether a new approach involving the reductive desulfurization of (11aS)1,2,3,10,11,11a-hexahydro-5H-pyrrolo[2,1-*c*][1-4]benzodiazepine-5-one-11-thione (**8**), by Raney nickel in ethanol. The monothiodilactams (**8**) have been prepared by thiation of the PBD dilactams (**7**) employing Lawesson's reagent. These dilactams in turn have been prepared by the cyclocondensation of isatoic anhydride (**5**) with L-proline (**6**), or by the reductive cyclization of methyl(2S)-N-(2-nitrobenzoyl)pyrrolidine-2-carboxylates (**2**) . The cyclic secondary amines **4** upon oxidation with catalytic amount of TPAP and two equivalents of N-methylmorpholine N-oxide (NMO) as a co-oxidant gave the corresponding PBD imines **9a** and **9b** in 40% and 60% yields respectively.



4 **9**

a) $R_1 = R_2 = H$, b) $R_1 = OH$, $R_2 = OCH_3$

Scheme-3

This methodology has also been extended towards the synthesis of the natural product DC-81 to illustrate the generality of this oxidative procedure employing TPAP. It is well kown that all biologically active PBDs possess the (S)-configuration at the C11a position which provides the molecule with a right handed twist when viewed from the C-ring towards the A-ring, thus providing the appropriate three dimensional shape for a snug fit within the minor groove of DNA. In contrast, to the usual methods which involve simultaneous cyclization with imine formation, in the present oxidative route there is less chance of racemization at the C11a position. The most significant advantage of using TPAP rather than activated DMSO as reported previously[7] is the complete absence of side-products. Furthermore, this method avoids aqueous work up for the sensitive imine moiety.

Conclusion: This new mild oxidation of secondary amine to imine by TPAP avoids cumbersome protective and deprotective techniques. In this approach there is less opportunity for racemization at C11a position as compared to the previously reported deprotective and reductive cyclizations[4d,4k]. Thus, the method described above offers a simple, convenient and useful procedure for the synthesis of natural and synthetic PBDs.

Experimental

All the reactions were carried out under anhydrous conditions and in nitrogen atmosphere unless and otherwise stated. All the solvents were purified or dried according to the standard literature procedure. THF was distilled over sodium and benzophenone ketyl prior to use. CH_2Cl_2 was distilled from P_2O_5. All the reactions were monitored by thin layer chromatography (TLC) carried out on precoated 0.2 mm E.Merck silica gel plates (60 F_{254}) with uv light, iodine as developing agents. Acme India silica gel (finer than 200 mesh) was used for flash chromatography. Melting points were determined on a Fisher-Johns melting point apparatus and were uncorrected. Optical rotations were measured on Jasco Dip 360 digital polarimeter. Infrared spectra were recorded on a Perkin-Elmer 683 or1310 spectrometer. ^1H and ^{13}C NMR spectra were recorded on Bruker WH 300 or Varian Gemini 200 MHz spectrometer. The chemical shifts are expressed in ppm relative to TMS and coupling constants are in Hz. Mass spectra (ms) were recorded on CEC-21-110B, Finnigan Mat 1210 or Micro Mass-7070 spectrometers operating at 70 ev using a direct inlet system.

Methyl(2S)-N-(2-nitrobenzoyl)pyrrolidine-2-carboxylate (2a)

DMF was added to a stirred suspension of compound **1a** (5 gm. 15.6 mmol) and thionyl chloride (8 ml) in dry benzene (30 ml) and the stirring was continued for 3h. The benzene was evaporated in vacuo and the resultant oil dissolved in dry THF (25-30 ml). This was added dropwise over a period of 30 min to a stirred solution of (2S)-proline methylester hydrocholride (2.05 gm. 15.6 mmol) and triethylamine (3.15 gm, 31.2 mmol, 2 eq) cooled in an ice bath at 0°C. After the completion of the addition the mixture was brought to room temperature and stirred for an additional hour. The THF was evaporated and the residue is redissolved in ethylacetate then adjusted to pH3 (with 10% HCl) and extracted with ethylacetate (2x20 ml). Then the organic layer was seperated from the aqueous layer. The combined organic phases were washed with brine, dried over $MgSO_4$ and evaporated in vacuum to afford the corresponding compound **2a**. $[\alpha]^D_{27}$ -121.26 (c 0.5. $CHCl_3$)

^{1}HNMR: ($CDCl_3$) δ 1.86-2.52 (m,4H), 3.21-3.47 (m,2H), 3.88 (d,3H), 4.6 (dd,1H, J=8.0 and 4.2 Hz), 7.21-7.62 (m,3H), 8.10 (d,1H, J=6.2 Hz).

IR: ($CHCl_3$) 1740, 1630, 1585, 1475, 1440, 1245, 1200, 1173, 1045, 860, 775, 745 cm^{-1}.

MS: m/e 278 ($m^{+\cdot}$,2) 219, 150 (100), 134, 128, 120, 104, 92, 76.

Methyl(2S)-N-(4-hydroxy-5-methoxy-2-nitrobenzoyl)pyrrolidone-2-carboxylate (2b)

^{1}HNMR: ($CDCl_3$) δ 1.94-2.18 (m,3H), 2.21-2.30 (m,1H), 3.18-3.39 (m,2H), 3.79 (s,3H), 3.98 (s,3H), 4.69-4.73 (m,1H), 6.78 (s,1H), 6.92 (s,1H), 7.66 (s,1H).

IR: ($CHCl_3$) 3200-2800, 1740, 1630, 1575, 1510, 1485, 1348, 1270, 1230, 1150, 1050, 750 cm^{-1}.

MS: m/e 324 ($m^{+\cdot}$,14).

(2S)-N-(2-Nitrobenzoyl)pyrrolidine-2-carboxaldehyde (3a)

DIBAL-H solution (2.05 ml of a 1M solution in hexane, 3 mmol, 2.02 eq) was added dropwise over

a period of 10 min to a vigorously stirred solution of the methyl(2S)-N-(2-nitrobenzoyl)pyrrolidine-2-carboxylate (**2a**) (278 mg, 1 mmol, 1 eq) in anhydrous CH_2Cl_2 (10 ml) under dry nitrogen at -78°C (dry-ice/acetone bath). After the mixture was stirred for an additional 30 min excess reagent was decomposed by careful addition of methanol (15-20 ml) followed by 5% HCl (5 ml). The resulting mixture was allowed to warm to 0°C and the organic layer was then removed. The aqueous layer was extracted with CH_2Cl_2 (2x15 ml). The organic layers were combined, washed with brine and dried over $MgSO_4$. Finally, the solvent was evaporated in vacuum to afford the compound **3a** in 55% yield. $[\alpha]^{D}_{27}$-146.9 (c 0.049, $CHCl_3$)

^{1}HNMR ($CDCl_3$) δ 1.70-2.5 (m,4H), 3.05-3.50 (m,2H), 4.30-4.80 (m,1H). 7.12-8.29 (m,4H), 9.82 (d,1H 4.2 Hz).

IR: ($CHCl_3$) 1730, 1640, 1530, 1478, 1340 cm^{-1}.

MS: m/e 248 (m^+,30) 219, 200, 185, 171, 150, 104, 76.

(2S)-N-(4-Hydroxy-5-methoxy-2-nitrobenzoyl)pyrrolidine-2-carboxaldehyde (3b)

^{1}HNMR: ($CDCl_3$) δ 1.88-1.97 (m,2H), 2.10-2.24 (m,2H), 3.98 (s,3 H), 4.49 (t, 1H, J=6.3 Hz), 6.92 (s,1H), 7.59 (s,1H), 9.79 (d,1H, J=6.2 Hz).

^{13}CNMR: ($CDCl_3$) δ 24.7, 26.3, 48.0, 55.7, 64.2, 71.2, 110.2 111.8, 135.4, 137.6, 148.2, 153.2, 166.2, 198.7.

IR: (KBr) 1725, 1620, 1575, 1510, 1475, 1358, 1273, 1248, 1050, 975, 860, 750 cm^{-1}.

MS: m/e 265 (m^+,30).

(11aS)-1,2,3,10,11,11a-Hexahydro-5H-pyrrolo[2,1-*c*][1,4]benzodiazepine-5-one (4a)

The nitroaldehyde (**3**) (280 mg, 1.13 mmol) was dissolved in methanol (7.5 ml) and hydrogenated at atmospheric pressure over 10% Pd-C catalyst (100 mg) hydrogenation continued for 5h, until the TLC indicated a total conversion to the secondary amine (**4**). The reaction mixture was filtered through celite and evaporated to dryness in vacuo. The residue was purified by chromatography (silica gel), using ethylacetate-hexane (8:2) as an elutant to afford the secondary amine (**4**) as a pale yellow solid. (160 mg 70%).

The monothiodilactam (**8**) (232 mg, 1 mmol) was dissolved in 10 ml of ethanol and 2 ml of a slurry of Raney nickel in ethanol was added. The reaction mixture was refluxed for about 6h or until the TLC indicated the completion of the reaction. Then the reaction mixture was filtered and the filtrate concentrated to dryness to give rise to the PBD cyclic secondary amine (**4**) in good yields.

^{1}HNMR: ($CDCl_3$) δ 1.60-2.46 (m,4H), 3.22-4.01 (m,5H), 6.61-6.66 (d,1H, J=6.2 Hz), 6.80-6.92 (m,1H), 7.20-7.29 (m,1H), 8.01 (d,1H, J=5.2 Hz).

IR: (KBr) 3330, 2875, 1620, 1485, 1250, 1065, 945 cm^{-1}.

MS: m/e 202 (m^+,100), 133, 119, 105, 70.

(11aS)-8-Hydroxy-7-methoxy1,2,3,10,11,11a-hexahydro-5H-pyrrolo[2,1-*c*][1,4]benzodiazepine-5-one (4b)

^{1}HNMR: ($CDCl_3$) δ 1.42-2.38 (m,4H), 3.19-3.29 (m,1H), 3.50-3.59 (m,1H), 3.62-3.79 (m,3H), 3.92 (s,3H), 6.20 (s,1H), 7.62 (s,1H).

IR: (KBr) 3320, 2875, 1615, 1475, 1050, 980, 765 cm^{-1}.

MS: m/e 248 ($m^{+\cdot}$,100), 231, 179, 165, 98, 75, 48.

(11aS)-1,2,3,11a-Tetrahydro-5H-pyrrolo[2,1-*c*][1,4]benzodiazepine-5-one (9a)

To a solution of the cyclic secondary amine 4a (101 mg; 0.5 mmol) in acetonitrile (5 ml) was added 4A° powdered molecular sieves (250 mg), NMO (132 mg; 1.0 mmol), TPAP (18 mg; 0.05 mmol) and stirred at room temperature for 1.5h. On completion of the reaction, the acetonitrile was removed under vacuum. The reaction mixture was then taken up in ethylacetate and filtered through a silica pad eluting with ethylacetate. The filtrate was evaporated and the residue purified by flash chromatography (silica, ethylacetate) to afford the PBD imine **5a** as a light yellow oil (yield 40%) $[\alpha]^{D}_{27}$ +316 (c 0.5 $CHCL_3$).

^{1}HNMR: ($CDCl_3$) δ 1.91-2.37 (m,4H), 3.51-3.92 (m,3H), 7.28-7.56 (m, 3H), 7.78 (d,1H, J=4.6 Hz) 8.05 (d,1H, J=5.2 Hz)

IR: ($CHCl_3$) 3320, 2970, 2875, 1615, 1575, 1480, 1460, 1255, 1160, 1120, 1025, 878, 830 cm^{-1}.

MS: m/e 200 ($M^{+\cdot}$, 100), 171, 160, 144, 120, 103, 83, 70.

HRMS: Calc. for 200.0950 ($C_{12}H_{12}ON_2$) found 200.0936

(11aS)-8-Hydroxy-7-methoxy-1,2,3,11a, tetrahydro-5H-pyrrolo[2,1,-*c*][1,4]benzodiazipne-5-one (9b)

^{1}HNMR: ($CDCl_3$) δ 1.95-2.05 (m,2H), 2.27-2.35 (m,2H), 3.50-3.95 (m,3H), 3.98 (s,3H), 6.89 (s,1H), 6.92 (b,1H), 7.49 (b,1H), 7.69 (d,1H, J=4.2 Hz).

^{13}CNMR: ($CDCl_3$) δ 24.1, 29.6, 46.2, 53.8, 55.9, 111.6, 112.8, 118.6, 139.2, 143.6, 148.9, 158.2, 166.8.

MS: m/e 246 ($m^{+\cdot}$, 100), 217, 203, 150, 122, 103, 70.

HRMS: Calc for 246.1004 $C_{13}H_{14}N_2O_3$, found 246. 1002.

(11aS)-1,2,3,10,11,11a-Hexahydro-5H-pyrolo[2,1-*c*][1,4]benzodiazepine 5,11-dione (7a)

Isatoic anhydride (**5**) (1.63 gm. 10 mmol) and L-proline (**6**) (1.23 gm. 10.7 mmol) was dissolved in DMF (20 ml) and heated under reflux for 4h. More than half of DMF was distilled off under vacuum to which was added crushed ice (30 gm). The resulting precipitate was filtered off and recystallised from water to yield a white amorphous solid (78%).

The nitroester (**2a**) (472 mg, 1.7 mmol) was dissolved in methanol (10 ml) and 10% Pd-C (85 mg) was added. This mixture was hydrogenated at room temperature under atmospheric pressure for 1h or until TLC indicated that the reaction was complete. The catalyst was removed by filtration through celite and the solvent evaporated in vacuum to afford the compound **7a** in about 70% yield.

^{1}HNMR: ($CDCl_3$ + DMSO-d_6) δ 1.90-2.56 (m,4H), 3.30-3.52 (m,2H), 4.10 (1H, d, J=9.2 Hz), 7.08 (1H, d, J=7.9 Hz), 7.21 (1H, d, J=8.2 Hz), 7.57 (1H, d, J=9.1 Hz), 8.10 (1H, dd, J=6.1, 7.9 Hz), 10.2 (1H, s) (exchangeable with D_2O).

^{13}CNMR: ($CDCl_3$ + DMSO-d_6) δ 28.6, 29.2, 54.1, 55.2, 120.6, 123.1, 125.8, 130.1, 132.7, 136.2, 165. 6,170.1.

IR(KBr): 3440, 2360, 2930, 1675, 1625, 1580, 1490, 1452, 1425, 1375, 1220, 1095, 967, 765 cm^{-1}.

MS: m/e 232 (M^+, 21).

(11aS)-8-Hydroxy-7-methoxy-1,2,3,10,11,11a-hexahydro-5H-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (7b)

^{1}HNMR: ($CDCl_3$) δ 1.81-2.53 (m,4H), 3.32-3.56 (m,2H), 3.93 (s,3H), 4.22 (d,1H, J=7.2 Hz), 6.8 (s,1H), 7.14-7.42 (m,5H), 7.82 (s,1H).

IR (KBr): 3430, 3350, 3040, 1665, 1625, 1575, 1485, 1360, 1065 cm^{-1}.

MS: m/e 263 (m^+, 80). 233, 206, 192, 165, 150, 144, 105, 87, 70 (100), 68, 64.

(11aS)-1,2,3,10,11,11a-Hexahydro-5H-pyrrolo[2,1-*c*][1,4]benzodiazepine-5-oxo-11-thione (8a)

The PBD 5,11-dione (**7a**) (362 mg, 1.68 mmol) and the Lawesson's reagent (340 mg, 0.842 mmol) in 40ml of toluene was heated upto 70°C for 3-4h. After the completion of reaction by TLC the toluene was evaporated. The residue was chromatographed on silica gel column to give 86% yield of the title compound (**8a**).

1HNMR: ($CDCl_3$ + DMSO-d_6) δ 2.10-2.76 (m,4H), 3.22-3.48 (m,2H), 4.09 (d,1H, J=6.2 Hz), 7.18 (d,1H, J=9.2 Hz), 7.21 (d,1H, J=8.2 Hz) 7.52 (d,1H, J=9.2 Hz), 7.21 (d,1H, J=8.2 Hz) 7.52 (d,1H, J=9.2 Hz), 8.06 (d,1H, J=7.9 Hz), 11.12 (1H, brs. exchangeable with D_2O).

^{13}CNMR: ($CDCl_3$ + DMSO-d_6) δ 24.1, 28.2, 53.2, 55.1, 121.6, 124.9, 126.3, 127.2, 132.3, 135.1, 165.0, 195.0.

IR (KBr): 3450, 3240, 2880, 1630, 1585, 1490, 1485, 1410, 1360, 1240, 1098, 965, 760 cm^{-1}.

MS: m/e 232 (M^+, 100), 216, 199, 171, 162, 135, 108, 91, 70.

(11aS)-8-Hydroxy-7-methoxy-1,2,3,10,11,11a-hexahydro-5H-pyrrolo[2,1-*c*][1,4]benzodiazepine-5-one-11-thione (8b)

^{1}HNMR: ($CDCl_3$) δ 1.72 -2.46 (m,4H), 3.22-3.39 (m,2H), 3.90 (s,3H), 4.22 (d,1H, J=7.2 Hz), 6.30 (s, 1H) (exchangeable with D_2O) 6.92 (s,1H), 7.62 (s,1H), 10.05 (s,1H) (exchangeable with D_2O).

IR (KBr): 3430, 3280, 2990, 1625, 1485, 1360, 1280, 1160, 1075 cm^{-1}.

MS: m/e 278 (m^+, 54).

Acknowledgment: The authors are thankful to the British Council and CSIR, New Delhi for the support of a HEG Link Project. The Cancer Research Campaign is also thanked for financial support. BSPR is greatful to CSIR for the award of a Research Associateship and BSNR is thankful to UGC, New Delhi for the award of a Research Fellowship.

References

1. a) Thurston, D.E. "Advances in the study of Pyrrolo[2,1-*c*][1,4]benzodiazepine (PBD) Antitumour Antibiotics" in the "Molecular Aspects of Anticancer Drug-DNA Interactions", Neidle, S.; Waring, M. J. Eds.; Macmillan, 1993, Vol.1, pp. 54 - 88.
2. Hurley, L.H.; Needham-VanDevanter, D. R. *Acc. Chem. Res.* **1986**, *19*, 230.
3. a) Thurston, D.E.; Morris, S.J.; Hartley, J. A. *J. Chem. Soc. Chem. Commun.*, **1996**, 563. b)Hartley, J.A., Souhami, R.L. "DNA Sequence Specificity of Anticancer Agents", in Cancer Chemotherapy; Frontiers in Pharmacology and Therapeutics series, Hickman, J.A.; Tritton, T. Eds.; Blackwell Scientific Ltd., **1993**, pp.251-280.
4. a) Leimgruber, W.; Batcho, A.D.; Czajkowski, R. C. *J. Am. Chem. Soc.*, **1968**, *90*, 5641. b) Thurston, D.E.; Langley, D.R. *J. Org. Chem.*, **1986**, *51*, 705. c) Kaneko, T.; Wong, H.; Doyle, T.W. *Tetrahedron Lett.* **1983**, *24*, 5165. d) Bose D.S.; Jones, G.B.; Thurston, D.E. *Tetrahedron* **1992**, *48*, 751. e) Courtney, S.M.; Thurston, D.E. *Tetrahedron Lett.* **1993**, *34*, 5372. f) Weidner-Wells, M.A.; DeCamp, A.; Mazzocchi, P.H. *J. Org. Chem.*, **1989**, *54*, 5746. g) Mori, M.; Uozumi, Y.; Ban, Y. *J. Chem. Soc. Chem. Commn.*, **1986**, 841. h) Molina,P.;Diaz, I.; Tarraga, A.,*Tetrahedron* **1995**, *51*, 5617. i) Wilson S.C.; Howard P.W.; Thurston D.E. *Tetrahedron Lett.* **1995**, *36*, 6333. j) Kraus, G.A.; Liu, P. *Tetrahedron Lett.* **1995**, *36*, 7595. k) Kamal, A.; Reddy, B.S.P.; Reddy, B.S.N. *Tetrahedron Lett.* **1996**, *37*, 2281.
5. Thurston D.E.; Bose, D.S. *Chem. Rev.*, **1994**, *94*, 433.
6. a) Nishinaga, A.; Yamazaki S.; Matsuura, T. *Tetrahedron Lett.* **1988**, *29*, 4115. b) Murahashi S.I. *Pure Appl. Chem.* **1992**, *64*, 403.
7. Kamal, A.; Rao, N.V. *J. Chem. Soc. Chem., Commun.*, **1996**, 385.
8. Griffith, W.P.; Ley, S.V.; Whitcombe, G.P.; White, A.D. *J. Chem. Soc. Chem. Commun.*, **1987**, 1625.
9. a) Ley, S.V.; Norman, J.; Griffith, W.P.; Marsden, S.P. *Synthesis*, **1994**, 639. b) Griffith, W.P.; Ley, S.V. *Aldrichimica Acta* **1990**, *23*, 13.
10. For example: a) Nicolaou, K.C.; Claiborne, C.F.; Nantermet P.G.; Couldouros, E.A. Sorensen, E.J. *J. Am. Chem. Soc.* **1994**, *116*, 1591. b) Holton, R.A.; Somoza, C.; Kim, H.B.; Liang, F.; Beider, R.J.; Boatman, P.D.; Shindo, M.; Smith, C.C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthy, K.K.; Gentile, L.N.; Liu, J.H. *J. Am. Chem. Soc.*, **1994**, *116*, 1597. c) Knight, D.W.; Sibely, A.W. *Tetrahedron Lett.* **1993**, *34*, 6607.
11. Goti, A.; Romani, M. *Tetrahedron Lett.* **1994**, *35*, 6567.

(*Received in UK* 21 *November* 1996; *revised* 31 *December* 1996; *accepted* 9 *January* 1997)