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2-Amidinylindole-3-carbaldehydes: synthesis of new tetracyclic compounds containing the pyrrolo[1,2-*c*]1,4-diazepine ring

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Abstract—2-Amidinylindol-3-carbaldehydes bearing an α-alkoxycarbonyl substituent on the cyclic-tertiary amine moiety were prepared. Pyrolysis of these amidines in diethylenglycol-monoethyl ether produced mainly a pyrrolo[1′,2′-1,2]-1,4-diazepino[5,6-*b*]indol-7,11-dione. A similar result was obtained starting from 2-amidinylbenzofuran-3-carbaldehyde.

1. Introduction

The pyrrolo[1,2-*c*][1,4]-benzodiazepine ring system is part of the naturally-occurring DNA-interactive antitumor antibiotics known as the 'anthramycines'.[1] They are produced by various *Streptomyces* species and the biosynthesis of a number of pyrrolo[1,2-*c*][1,4]-benzodiazepine rings has been studied.[2] Numerous studies have demonstrated that anthramycin binds in the narrow groove of DNA. The model proposed for attachment of anthramycin to DNA involves a covalent aminal linkage between the 2-amino group of the guanidine and C-11 of anthramycin,[3] and was confirmed by a NMR study of an anthramycin-DNA adduct[4] (Fig. 1). Starting from these data reported in the literature, the aim of our research was the synthesis of compounds containing the pyrrolo[1,2-*c*]1,4-diazepine ring and heterocyclic nuclei.

A previous paper[5] was dedicated to studying the utilisation of 2-amidinylindole-3-carbaldehydes in the synthesis of α-carbolines. Particularly, we found that acid-catalysed pyrolysis of the above amidines produced, as well as the anticipated 3,9-dialkyl-2-morpholino-pyrido[2,3-*b*]indoles, a significant amount (50%) of the unexpected 2-amino-3-indolecarboxamides.[5] Preliminary investigation on the reactivity of this by-product prompted us to investigate the reaction pathway with the aim of establishing the best reaction conditions to favour its formation. In fact the primary amino group, in position 2 on the indole had shown remarkable reactivity with carbonylic group. Therefore, if a carbonylic function had been present in the α-position of the tertiary amine, the primary amino group would have reacted with it, resulting in formation of a new heterocyclic ring on the indole moiety. The retrosynthetic pathway is indicated in Scheme 1. A tetracyclic system containing the 1,4-diazepinedione ring **A** could be obtained from amidines C through indolecarboxamide B. Compounds containing the 1,4-diazepinedione ring condensed with the indole moiety have not been described previously. The resemblance of this structure to the 'anthramycines' caused us to investigate this synthetic strategy.

2. Results and discussion

Our plan was to synthesise amidines **1a**,**b** with an α-alkoxycarbonyl substituent on the cyclic-tertiary amine moiety. The alkoxycarbonyl group was chosen because of its ability to react intramolecularly with the amino group of the 2-amino-3-indolecarboxamide residue.

The amidines **1a**,**b** were directly obtained in good yields by reacting 1-benzyl-2-azido-indol-3-carbaldehyde **2**[5] in an inert solvent with propionaldehyde **3** and L-methylprolinate **4a** or L-methylthiazolidin-3-carboxylate **4b** (Scheme 2). Acid-catalysed transformation of amidine **1a** (SiO_2, 180°C) produced two different compounds. One was easily identified as α-carboline **5** by analogy with previous results.[5] The other was identified as pyrrolo[1′,2′-1,2]-1,4-diazepino[5,6-*b*]indol-7,11-dione **6a**. The products **5** and **6a**

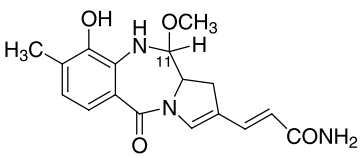

Figure 1. Structure of anthramycin methyl ether.

Keywords: amidines; anthramycin; pyrrolo[1,2-*c*]-1,4-diazepine; intramolecular cyclization.

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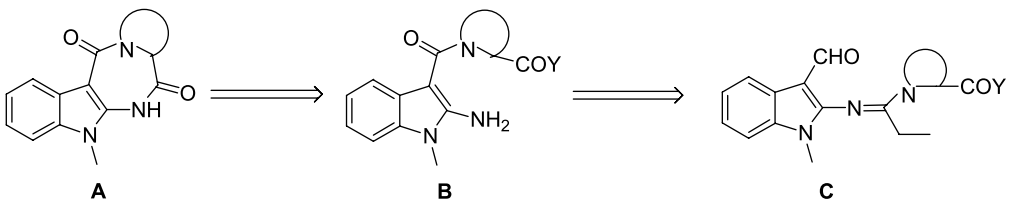


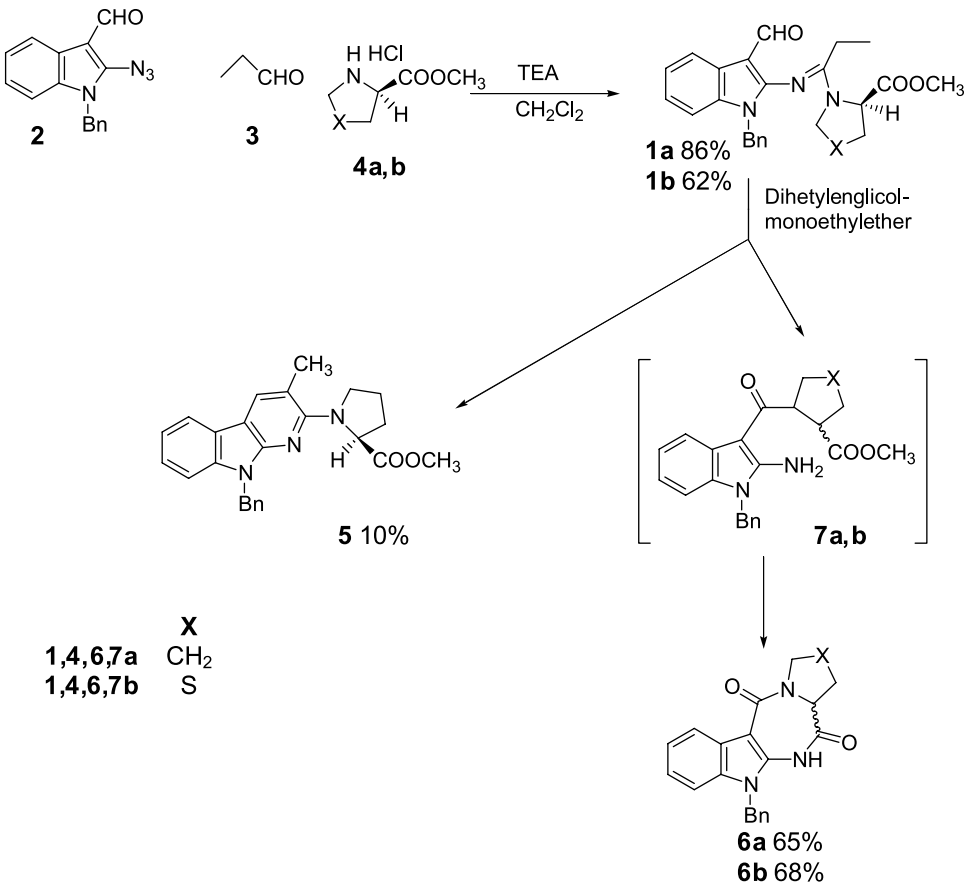
Scheme 1.

were obtained in 50 and 50% yields, respectively. This result was explained through the primary formation of 2-amino-3-indolecarboxamide **7a**, followed by immediate intramolecular condensation of the amino and the methoxycarbonyl group (Scheme 2). Compound **6a** did not show optical activity because it racemized under these reaction conditions.

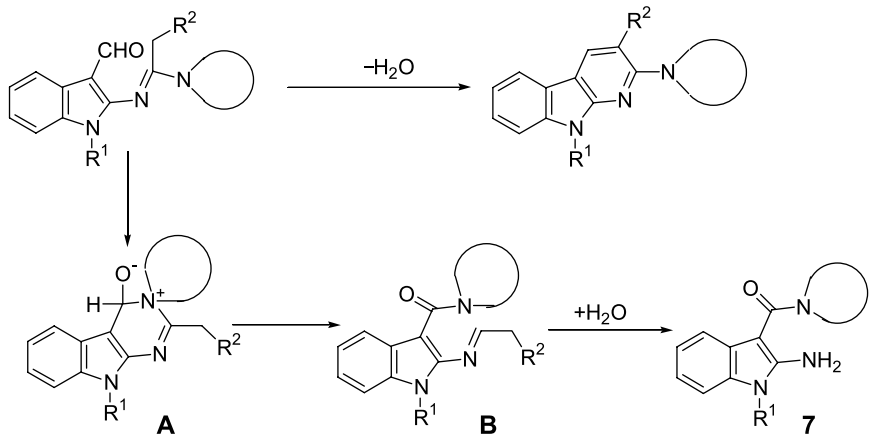
The unsatisfactory yield of product **6a** drove us to change the reaction conditions. The supposed reaction mechanism of the rearrangement of **2** to **7** is reported in Scheme 3. The origin of intermediate **7** is explained assuming the formation of a cyclic ammonium intermediate (**A**) which produces an imine (**B**) by ring opening. Subsequent hydrolysis of (**B**) gives the final product **7**. The reaction conditions are anhydrous (180°C without any solvent) and the required water was probably supplied by the parallel condensation forming the α-carboline **5**. Several conditions were investigated and the best involved using diethylenglycol-monoethylether (DEGMEE) as the solvent at reflux. This solvent was chosen due to its high boiling point (189°C) and to aid the hydrolysis process. As a result, the yield of **6a** was increased (65% of isolated product) and the amount of the by-product **5** was significantly reduced. Similar good results were obtained in the case of amidine **1b**, which afforded exclusively the desired tetracyclic compound **6b** under identical reaction conditions (68% yield).

The structure of compound **6a** was confirmed by its analytical and spectroscopic data. The ^{1}H NMR spectrum shows a broad singlet at about δ 9.00 (exchangeable), an AB system at δ 5.40 associated with the methylene protons of the benzyl group and the expected signals associated with the pyrrole and indole moieties. In the ^{13}C NMR spectrum two singlets at δ 169.3, 163.0 associated with N–C═O and at δ 99.3 associated with N–C–NH[3] were the most important features.

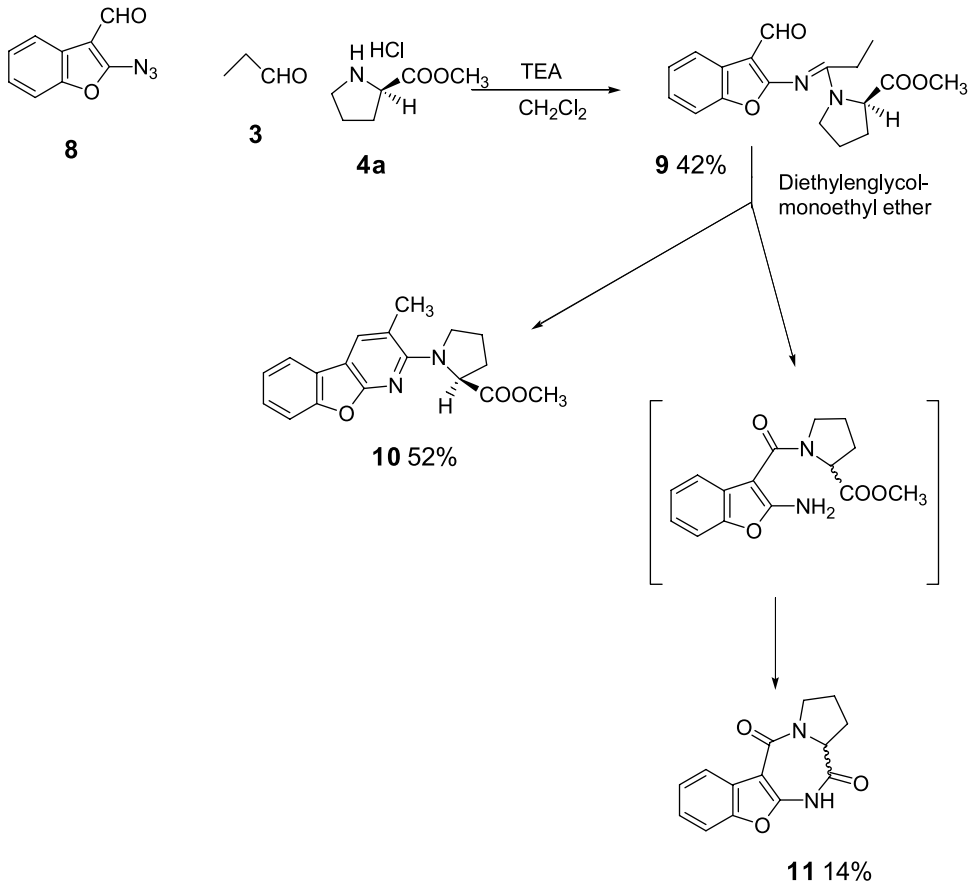
These encouraging results prompted us to extend the reaction to 2-azido-benzofuran-3-carbaldehyde **8**.[6] This



Scheme 2.



Scheme 3.



Scheme 4.

ortho-azido carbaldehyde easily prepared by the literature method reacted with methylprolinate and propionaldehyde yielding the expected amidine **9** (Scheme 4). The transformation reaction of amidine **9** in DEGMEE yielded the benzofuran[2,3-*b*]pyridine derivative **10** as the main product (52%) together with a minor amount (14%) of the tetracyclic compound **11** (Scheme 4).

In conclusion, readily available starting materials have been successfully used to develop synthetic pathways directed toward new compounds containing the pyrrolo[1,2-*c*]1,4-diazepine ring together with a heterocyclic nucleus, that have not previously been described.

3. Experimental

Mps were determined by a Büchi 510 (capillary) apparatus. $[\alpha]_D$ values were measured with Perkin–Elmer 343 plus polarimeter (*c* 10% in $CHCl_3$). IR spectra were measured with a JASCO IR Report 100 instrument (Nujol; cm^{-1}). NMR spectra were obtained with Bruker Advance 300, Bruker AC 200 and Varian Gemini 200 instruments. *J* values are given in Hz for solutions in $CDCl_3$. 1-Benzyl-2-azido-1*H*-indole-3-carbaldehyde **3**[5] and 2-azido-benzofuran-3-carbaldehyde **8**[6] are known compounds and were prepared according to the literature procedures.

3.1. Synthesis of amidines 1a,b and 9. General procedure

Ester hydrochlorides **4a**,**b** (50 mmol) were suspended in CH_2Cl_2 (50 mL) and TEA (50 mmol) was added. Then azides **2** or **8** (50 mmol) and propionaldehyde **3** (50 mmol) were added in one portion. The solution was stirred until disappearance of the starting material (TLC: ethyl acetate–cyclohexane (3:7); 48 h). The solvent was evaporated and the crude product was purified by chromatography (ethyl acetate–cyclohexane (2:3 to 9:1)).

3.1.1. 1-[1-(1-Benzyl-3-formyl-1*H*-indol-2-ylimino)-propyl]-pyrrolidine-2-carboxylic acid methyl ester 1a. Yield 86%. Mp 162°C (white crystals from EtOH). $[\alpha]_D^{20}=-271.2$. IR 1640, 1735 (C═O), ^{1}H NMR 0.98 (3H, t, J=7.2 Hz, CH_3), 1.99–2.65 (6H, m, CH_2), 3.36 (3H, s, OCH_3), 3.61–3.78 (2H, m, CH_2N), 4.69 (1H, m, CHCOO), 4.98 (1H, d, J=16.1 Hz, C*H*HPh), 5.22 (1H, d, J=16.1 Hz, CH*H*Ph), 7.08–7.33 (8H, m, ArH), 8.17–8.20 (1H, d, J=6.3 Hz, H-4), 9.67 (1H, s, CHO), ^{13}C NMR 10.8q, 23.5t, 24.8t, 29.4t, 45.4t, 47.8t, 51.9d, 60.3q, 103.8s, 109.4d, 120.1d, 122.0d, 122.3d, 126.0s, 127.0d, 127.5d, 128.7d, 134.8s, 137.0s, 137.0s, 164.4, 172.8s, 183.3d. Calcd for $C_{25}H_{27}N_3O_3$ (417.50) C 71.92 H 6.52 N 10.06. Found C 71.84 H 6.62 N 9.94.

3.1.2. 3-[1-(1-Benzyl-3-formyl-1*H*-indolylimino)-propyl]-thiazolidine-4-carboxylic acid methyl ester 1b. Yield 62%. Mp 132°C (white crystals from EtOH). $[\alpha]_D^{20}=-267.8$. IR 1640, 1720 C═O, ^{1}H NMR 1.17 (3H, t, J=7.2 Hz, CH_3), 2.30–2.54 (2H, m, CH_2), 3.28–3.72 (5H, m, CH_3O and SCH_2), 4.73 (2H, s, SCH_2N), 5.73–5.24 (3H, m, CH_2Ph and CHCOO), 7.14–7.34 (8H, m, ArH), 8.20 (1H, d, J=6.4 Hz, H-4), 9.73 (1H, s, CHO), ^{13}C NMR 11.0q, 23.9t, 33.3t, 45.6t, 49.9t, 52.6d, 62.6q, 103.9s, 109.5d, 120.3d, 122.2d, 122.5d, 125.9s, 127.0d, 127.6d, 128.8d, 134.8s, 136.8s, 136.8s, 164.0s, 170.4s, 184.2d. Calcd for $C_{24}H_{25}N_3O_3S$ (435.54) C 66.18 H 5.79 N 9.65. Found C 66.24 H 5.97 N 9.35.

3.1.3. 1-[1-(3-Formyl-benzofuran2-ylimino)-propyl]-pyrrolidin-2-carboxylic acid methyl ester 9. Yield 42%. (Red oil). $[\alpha]_D^{20}=-195.9$. IR 1640, 1735 (C═O), ^{1}H NMR 1.14–1.37 (3H, m, CH_3), 2.05–2.89 (6H, m, $3CH_2$), 3.69–3.89 (5H, m, CH_3O and CH_3N), 4.70–4.77 (1H, m, CH–COO), 7.13–7.36 (3H, m, ArH), 8.06 (1H, d, H-4), 9.97 (1H, s, CHO), ^{13}C NMR 10.9q, 24.7t, 25.8t, 29.3t, 48.0t, 52.5d, 61.1q, 105.7s, 109.8s, 110.0, 120.9d, 123.3d, 124.1d, 126.0s, 150.6s, 164.9s, 172.6s, 185.9s. Calcd for $C_{18}H_{20}N_2O_4$ (328.36) C 65.84 H 6.14 N 8.53. Found C 65.64 H 6.22 N 8.34.

3.2. Pyrolysis of amidines 1a,b and 9. General procedure

Compound **1a**,**b** or **9** (2 mmol) was dissolved in DEGMEE (2 mL) and refluxed in an oil bath. Heating was continued until disappearance of the starting material (TLC: ethyl acetate–cyclohexane (7:3) (5–12 h)). The mixture was evaporated at reduced pressure and acetone (5–6 mL) was added. Products **6a**,**b** or **11** crystallized from acetone and were collected by filtration. The residue was evaporated and purified by chromatography (ethyl acetate–cyclohexane (1:4)) to supply the products indicated in Schemes 2 and 4.

3.2.1. 5-Benzyl-5,6,7,7a,8,9,10,11-octhahydro-pyrrol-[1′,2′-1,2]-1,4-diazepino-[5,6-*b*]-indol-7,11-dione 6a. Reaction time 6 h. Yield 65%. Mp 278°C (pale yellow crystals from acetone). IR 1640 (C═O), ^{1}H NMR 1.66–2.58 (4H, m, $2CH_2$), 3.68–3.73 (2H, m, CH_2N), 4.13–4.21 (1H, m, CHN), 5.22 (1H, d, J=16.8 Hz, C*H*HPh), 5.52 (1H, d, J=16.8 Hz, CH*H*Ph), 7.00–7.35 (8H, m, ArH), 8.22–8.26 (1H, m, H-1), 8.95 (1H, bs, NH), ^{13}C NMR 23.4t, 25.8t, 45.0t, 46.0t, 57.4d, 99.3s, 110.1d, 120.2d, 121.2d, 122.0, 125.5s, 126.2d, 127.2d, 128.6d, 133.8s, 136.8s, 136.8s, 163.0s, 169.3s. Calcd for $C_{21}H_{19}N_3O_2$ (345.39) C 73.03 H 5.54 N 12.17. Found C 72.78 C 5.59 N 11.47.

3.2.2. 1-(9-Benzyl-3-methyl-9*H*-pyrido[2,3-*b*]-indol-2-yl)-pyrrolidine-2-carboxylic acid methyl ester 5. Yield 10%. Mp 156°C (white crystals from EtOH). $[\alpha]_D=-148.9$. IR 1735 (C═O), ^{1}H NMR 1.96–2.34 (4H, m, $2CH_2$), 2.57 (3H, s, CH_3-3), 3.41 (3H, s, CH_3O), 3.78–4.10 (2H, m, CH_2N), 4.70–4.77 (1H, m, CH), 5.42 (1H, d, J=15.75 Hz, C*H*HPh), 5.65 (1H, d, J=15.75 Hz, CH*H*Ph), 7.13–7.30 (8H, m, ArH), 7.86–7.94 (1H, d, H-5), 7.95 (1H, s, H-4), ^{13}C NMR 20.9q, 25.4t, 29.1t, 44.8t, 50.4t, 51.5d, 62.7q, 107.5s, 109.4d, 111.3s, 119.3d, 119.5d, 121.7s, 123.9d, 127.1d, 128.6d, 132.7d, 138.3s, 138.5s, 149.0s, 156.0s, 175.5s. Calcd for $C_{25}H_{25}N_3O_2$ (399.49) C 75.16 H 6.31 N 10.52. Found C 74.92 H 6.54 N 10.29.

3.2.3. 6-Benzyl-1,3,3a,4,5,6,11-heptahydrothiazolo-[3′,4′-1,2]-1,4-diazepino-[5,6-*b*]-indol-4,11-dione 6b. Reaction time 12 h. Yield 68%. 265–267°C (pale yellow crystals from acetone). IR 1680 (C═O), ^{1}H NMR 3.16 (1H, dd, J=12.5, 6.7 Hz, CHS), 3.55 (1H, dd, J=12.5, 4.0 Hz), 4.35 (1H, dd, J=4.0, 6.7 Hz, CHN), 5.08 (2H, m, CH_2S), 5.32 (1H, d, J=15.38 Hz, C*H*HPh), 5.47 (1H, d, J=15.38 Hz, CH*H*Ph), 6.98–7.35 (8H, m, ArH), 8.22 (1H, d, J=1.7 Hz, H-10), 9.46 (1H, bs, NH), ^{13}C NMR (DMSO) 31.1t, 45.1t, 48.8t, 59.4d, 98.3s, 110.3d, 120.2d, 121.5d, 122.2d, 125.5s, 126.3d, 127.2d, 128.6d, 133.8s, 136.6s, 137.2s, 162.58s, 168.3s. Calcd for $C_{20}H_{17}N_3O_2S$ (363.43) C 66.10 H 4.71 N 11.56. Found C 65.87 H 4.96 N 11.24.

3.2.4. 1-(3-Methyl-benzo[4,5]furo[2,3-*b*]pyridin-2-yl)pyrrolidine-2-carboxylic acid methyl ester 10. Reaction time 5 h. Yield 52%. Mp 93°C (white crystals from EtOH). $[\alpha]_D=-157.5$. IR 1735 (C═O), ^{1}H NMR 2.02–2.36 (4H, m, CH_2–CH_2), 2.53 (3H, s, CH_3-3), 3.76 (3H, s, CH_3O), 3.81–4.02 (2H, m, CH_2N), 4.82–4.89 (1H, m, CHN), 7.26–7.54 (3H, m, ArH), 7.71–7.75 (1H, m, H-5), 7.84 (1H, s, H-4), ^{13}C NMR 20.7q, 25.3t, 29.4t, 50.8t, 52.1d, 62.0q, 107.1s, 111.5d, 115.1s, 115.1s, 119.5d, 122.8d, 123.8s, 125.3d, 133.5d, 153.7s, 156.5s, 174.9s. Calcd for $C_{18}H_{18}N_2O_3$ (309.14) C 69.66 H 5.85 N 9.03. Found C 69.52 H 5.95 N 8.94.

3.2.5. 6,7,7a,8,9,10,11-Heptahydropyrrolo[2′-1′1,2]-1,4-diazepino[5,6-*b*]-benzofuran-7,11-dione 11. Yield 14%. Mp 267°C (pal yellow crystals from acetone). IR 1620 (C═O). ^{1}H NMR 2.06–2.84 (4H, m, CH_2–CH_2), 3.62–3.82 (2H, m, CH_2N), 4.23–4.27 (1H, m, CHN), 7.26–7.43 (3H, m, ArH) 8.05 (1H, d, H-1), 9.95 (1H, bs, NH); ^{13}C NMR (DMSO) 24.1t, 26.5t, 46.9t, 58.8d, 99.5s, 111.4d, 121.3d, 124.6d, 124.8d, 127.3s, 150.6s, 152.3s, 162.4s, 169.2s; Calcd for $C_{14}H_{12}N_2O_3$ (256.26) C 65.62 H 4.72 N 10.93. Found C 65.45 H 4.91 N 10.81.

References

1. Thurston, D. E.; Subhas Bose, D. *Chem. Rev.* **1994**, *94*, 433–465, and the references cited therein.
2. (a) Hurley, L. H. *Acc. Chem. Res.* **1980**, *13*, 263. (b) Hurley, L. H.; Speedie, M. K. *Antibiot. IV. Biosynth.* **1981**, 261–294.
3. (a) Hurley, L. H.; Petrusek, R. L. *Nature* (*Lond.*). **282**, 529–531. (b) Petrusek, R. L.; Anderson, G. L.; Garner, T. F.; Fannin, Q. L.; Kaplan, D. J.; Zimmer, S. G.; Hurley, L. H. *Biochemistry* **1981**, *20*, 1111–1119.
4. Graves, E. G.; Pattaroni, C.; Krishnan, B. S.; Ostrander, J. M.; Hurley, L. H.; Krugh, T. R. *J. Biol. Chem.* **1984**, 8202–8209.
5. Erba, E.; Gelmi, M. L.; Pocar, D. *Tetrahedron* **2000**, *56*, 9991–9997.
6. Becher, J.; Pluta, K.; Krake, N.; Browdum, K.; Christensen, N. J.; Vinader, M. V. *Synthesis* **1989**, *7*, 530.