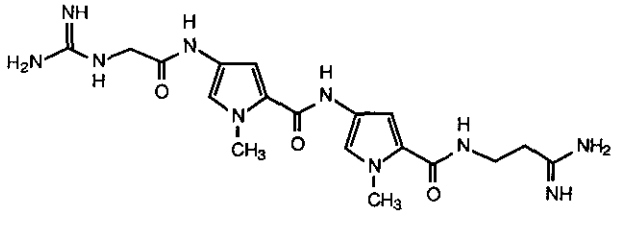
EFFICIENT SYNTHESIS OF OLIGO-N-METHYLPYRROLECARBOXAMIDES AND RELATED COMPOUNDS

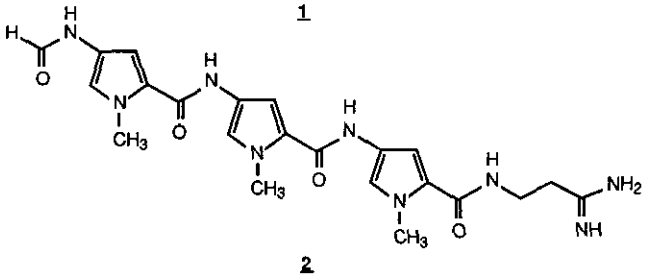
Eiji Nishiwaki, Shigeaki Tanaka, Hideaki Lee, and Masayuki Shibuya*
Faculty of Pharmaceutical Sciences, The University of Tokushima, Sho-machi 1, Tokushima 770, Japan

Abstract —— 1-Methyl-4-nitro-2-trichloroacetylpyrrole 5, a new precursor for the syntheses of oligo-N-methylpyrrolecarboxamide antibiotics and their analogues, was prepared with facility. The versatility of 5 was demonstrated by the syntheses of oligopeptides 16-19. 1-Methyl-4-nitro-2-trichloroacetylimidazole 8 was also prepared for a precursor of oligo-N-methylimidazolecarboxamides.

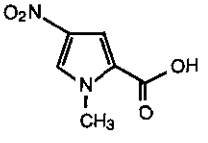
Netropsin 1[1] and distamycin 2[2] that contain N-methylpyrrolecarboxamides belong to a well known class of oligopeptide antitumor antibiotics called "Lexitropsins". Preferential binding of these peptides in the minor groove of double-helical DNA at specific AT-rich regions in a non-intercalative fashion has been the subject of X-ray crystallographic[3,4] and physico-chemical[3,5] investigations. In the past decade, Dervan and co-workers have demonstrated that higher numbers of N-methylpyrrolecarboxamides in synthetic oligopeptides fit the natural twist of the B-DNA helix with increased sequence specificity.[6,7] Recently, Dickerson and co-workers examined the structural requirements for the molecular recognition of the peptides and predicted that the replacement of one or more pyrrole rings by imidazole or other appropriate heterocycle, should result in a rational alteration of base recognition from AT to GC.[8] Lown and co-workers have synthesized these novel oligopeptide analogues and confirmed the prediction.[9]



1



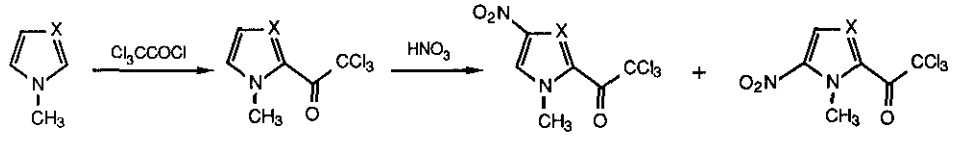
2



3

Not only because of above fundamental biological interest but also of therapeutic importance,[10] these natural oligopeptide antibiotics and related analogues have received considerable attention, and this has brought about the development of improved modifications[11] of the original syntheses.[12] All syntheses so far reported have utilized 1-methyl-4-nitropyrrole-2-carboxylic acid 3 as a starting material. The acid 3 was originally prepared by a five step route, starting from furane-2-carboxylic acid.[13] The disadvantages of the old route have been circumvented by simplified procedures starting from 1-methylpyrrole-2-carboxylic acid[11a] or its ester.[11b] Nitration method was improved recently for the preparation of 3, but the yield was not satisfactory.[11c]

Scheme 1.



4 X=CH
7 X=N

5 X=CH
8 X=N

6 X=CH
9 X=N

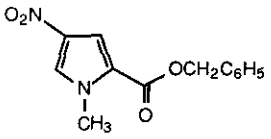
This paper presents a novel approach to the syntheses of the oligopeptides in which large scale starting material is available and the peptide formation process is simplified. The starting material used was 1-methyl-2-trichloroacetylpyrrole 4 which could be prepared from commercially available N-methylpyrrole by slightly modified Rapoport's method[14] in almost quantitative yield. Nitration of 4 was found to undergo nonregioselectively to give a mixture of 4-nitro and 5-nitro derivatives, which is similar to the result reported for the nitration of 2-trichloroacetylpyrrole,[15] but the desired 4-nitro isomer 5 was separable by quite simple work-up operations. When 4 was nitrated with 94% nitric acid-acetic anhydride mixture at -40°C, desired 1-methyl-4-nitro-2-trichloroacetylpyrrole 5 crystallized from the reaction mixture by adding isopropyl alcohol at -20°C. By a filtration and washing with isopropyl alcohol, pure 4-nitro isomer 5 was obtained in 63% yield. Extraction of the mother liquor and separation with column chromatography yielded an additional 5 (6% yield) along with 5-nitro isomer 6 (18% yield)(Scheme 1). Compound 5 is a white solid which can be stored at room temperature for months without any detectable deterioration, making it a convenient and versatile precursor for syntheses of various oligomers. The procedure is applicable to a preparation of the imidazole analogue 8. The starting trichloroacetylimidazole 7 was prepared by modified Regel's method[16] in good yield. Nitration of 7 was performed with fuming nitric acid-acetic anhydride mixture in the presence of catalytic amount of sulfuric acid at room temperature to give the desired 4-nitro isomer 8 almost exclusively. The structure of 8 was confirmed by leading it to known ethyl 1-methyl-4-nitroimidazole-2-carboxylate.[9b] It is known that the trichloroacetyl group can be converted to the acid, esters, or aliphatic amides with facility.[17] Thus, we carried out condensation reaction of 5 with various alcohols and amines, and the results are summarized in the following Table. We found that aromatic amines also react with 5 and 8 to give the corresponding amides.

Table. Condensation reactions of 5 with various alcohols and amines[a)]

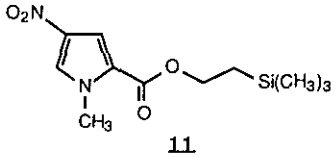
reagent	catalyst (mol. ratio)	temp. (°C)	time (min.)	product	yield[b)] (%)
benzyl alcohol	NaH(0.1)	20	45	10	98
2-trimethylsilylethyl alcohol	NaH(1.2)	0	5	11	83
3-aminopropionitrile	none	20	60	12	98
3,3-dimethylaminopropylamine	none	20	30	13	99
aniline	n-BuLi(1.05)	20	60	14	55
2,5-dimethoxyaniline	NaH(1.0)	20	10	15	63

a) All reactions were carried out in THF solution.

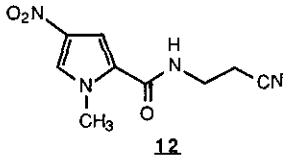
b) Isolated yields.



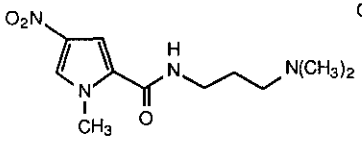
10



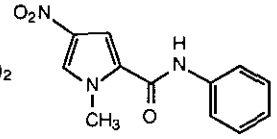
11



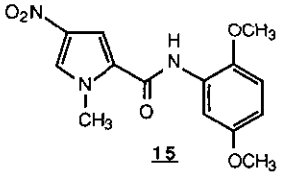
12



13



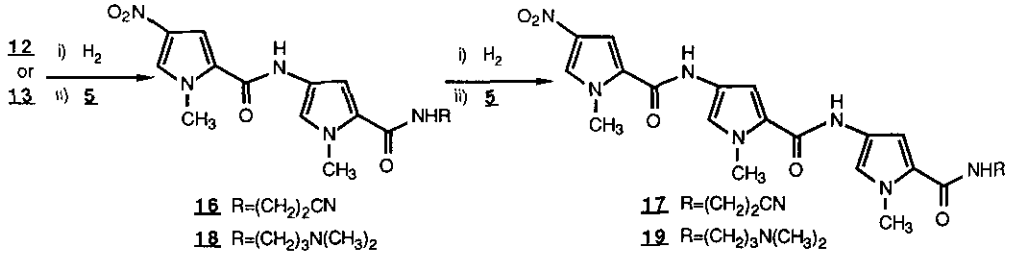
14



15

The present procedure provides a facile and versatile synthesis, on large scale, of a variety of oligo-N-methylpyrrolecarboxamides and related peptides without necessitating the use of relatively laborious operations for the usual peptide synthesis. In order to demonstrate this, oligopeptides 16-19 were synthesized as outlined in Scheme 2. The nitro group of the amide 12 was reduced to the amine which without any base catalyst was condensed with 5 to give the dipeptide 16. The reduction-condensation process was then repeated, leading to the tripeptide 17. Similarly, the peptides 18 and 19 were also synthesized. These oligopeptides 16-19 are the important precursors for the syntheses of various natural and unnatural oligo-N-methylpyrrolecarboxamides.[6,11a,c,18]

Scheme 2.



16 R=$(CH_2)_2CN$

18 R=$(CH_2)_3N(CH_3)_2$

17 R=$(CH_2)_2CN$

19 R=$(CH_2)_3N(CH_3)_2$

EXPERIMENTAL

Melting points were determined by the capillary method and uncorrected. Infra-red (Ir) spectra were determined with a Hitachi 215 spectrophotometer and ^{1}H-Nmr spectra with a JEOL JMS SP100

spectrometer or a JEOL JMS FX200 spectrometer using tetramethylsilane as an internal reference. Column chromatography was performed on silica gel (K-100-S, from Katayama Chemicals) throughout present study.

1-Methyl-2-trichloroacetylpyrrole (4).[14] To a solution of trichloroacetyl chloride (73g, 401mmol) in CH_2Cl_2 (240ml), was added a solution of N-methylpyrrole (32.447g, 400mmol) in CH_2Cl_2 (160ml) over a period of 3h. During this time, the reaction mixture was stirred vigorously and nitrogen was swept to remove HCl as it was formed. The solution was stirred overnight and then evaporated. The dark red residue was dissolved in $CHCl_3$ and filtered through a short column of silica gel. Evaporation of the solvent gave analytically pure pale yellow needles of 4 (90.570g, 100% yield); mp 65-66°C (lit.[17a] mp 64-65°C).

Nitration of 4. To a suspension of 4 (52.530g, 232mmol) in acetic anhydride (300ml) at -40°C, 19ml (1.8equiv) of 94% HNO_3 (d=1.50) was added over a period of 30min and then warmed up to room temperature. After stirring at room temperature for 2h, the mixture was cooled to -20°C. Isopropyl alcohol (300ml) was added and the resultant colorless solid was collected, washed with cold isopropyl alcohol, and dried under reduced pressure to give 4-nitro isomer 5 (39.521g, 63% yield); mp 135-140°C. Ir($CHCl_3$) 1690, 1510, 1330cm^{-1}. Nmr($CDCl_3$) δ 4.06(3H,s), 7.76(1H,d,J=1.7), 7.95(1H,d, J=1.7)ppm. Anal. Calcd for $C_7H_5Cl_3N_2O_3$(%): C,30.97; H,1.86; N,10.32. Found: C,30.96; H,1.85; N,10.31. The filtrate was extracted with AcOEt. The extract was washed with aqueous Na_2CO_3 and brine successively, dried over $MgSO_4$ and concentrated. The residue was chromatographed on silica gel. Elution with $CHCl_3$ gave additional 5 (3.802g, 6% yield) and the 5-nitro isomer 6 (11.300g, 18% yield). An analytical sample of 6 was prepared by recrystallization from n-hexane; mp 68-69°C. Ir($CHCl_3$) 1695, 1355, 1295cm^{-1}. Nmr($CDCl_3$) δ 4.28(3H,s), 7.16(1H,d,J=4.9), 7.44(1H,d,J=4.9)ppm. Anal. Calcd for $C_7H_5Cl_3N_2O_3$(%): C,30.97; H,1.86; N,10.32. Found: C,31.06; H,1.80; N,10.15.

1-Methyl-2-trichloroacetylimidazole (7). To a solution of trichloroacetyl chloride (73g, 401mmol) in CH_2Cl_2 (240ml), a solution of N-methylimidazole (32.850g, 400mmol) in CH_2Cl_2 (160ml) was added over a period of 2h. The solution was stirred for 6h at room temperature. During the time, precipitate (presumably, N-acylated imidazolium ion)[16] formed. The suspension was cooled to 0°C, and NEt_3 (40.5g, 400mmol) was added over a period of 1h, then evaporated. The residue was dissolved in $CHCl_3$ and filtered through a short column of silica gel. Evaporation of the solvent gave analytically pure pale yellow needles of 7 (73.100g, 80% yield); mp 79-80°C(lit.[16] mp 74°C). Ir($CHCl_3$) 1695, 1460, 1385cm^{-1}. Nmr($CDCl_3$) δ 4.07(3H,s), 7.17(1H,s), 7.36(1H,s)ppm. Anal. Calcd for $C_6H_5Cl_3N_2O$(%): C,31.68; H,2.22; N,12.31. Found: C,31.82; H,2.20; N,12.23.

Nitration of 7. Fuming HNO_3 (d=1.52, 4ml, 96mmol) was added dropwise to Ac_2O (50ml) at 0°C, and subsequently, conc. H_2SO_4 (0.1ml) was added to the mixture with stirring. Then 7 (6.820g, 30mmol) was added gradually to the solution with stirring at the same temperature. The resultant mixture

was warmed up to room temperature and stirred overnight, and extracted with $CHCl_3$. The extract was washed with aqueous $NaHCO_3$ and brine successively, then dried, filtered, and concentrated. The residual solid was recrystallized from $CHCl_3$ to give 8 (4.639g, 57% yield) as colorless plates. The mother liquor was concentrated and chromatographed on silica gel to give additional 8 (869mg, 11% yield) along with the 5-nitro isomer 9 (720mg, 9% yield). The 4-nitro isomer (8); mp 140-141°C. Ir($CHCl_3$) 1710, 1550, 1480, 1355cm^{-1}. Nmr($CDCl_3$) δ 4.17(3H,s), 7.97(1H,s)ppm. Anal. Calcd for $C_6H_4Cl_3N_3O_3$(%): C,26.45; H,1.48; N,15.42. Found: C,26.40; H,1.28; N,15.41. The 5-nitro isomer (9): mp 63-64°C. Ir($CHCl_3$) 1720, 1540, 1475, 1355cm^{-1}. Nmr($CDCl_3$) δ 4.38(3H,s), 8.12(1H,s)ppm. Anal. Calcd for $C_6H_4Cl_3N_3O_3$(%): C,26.45; H,1.48; N,15.42. Found: C,26.57; H,1.46; N,15.52. The smaller scale reaction gave a higher yield of 8. For example, nitration of 3mmol of 7 gave 8 in 86% yield. The 5-nitro isomer 9 was not detectable in the crude product.

Ethanolysis of 8. To a stirred suspension of 8 (244mg, 0.895mmol) in EtOH (10ml), catalytic amount of NaH was added at 0°C. The reaction mixture was warmed up to room temperature, stirred for 30min, and extracted with AcOEt. The extract was washed with brine, then dried, filtered, and concentrated. The residue was chromatographed on silica gel to give pale yellow needles of ethyl 1-methyl-4-nitroimidazole-2-carboxylate (136mg, 78% yield); mp 128-129°C (lit.[9b] mp 130-131°C). Spectroscopic data of this compound were identical with reported values.[9b]

Benzyl 1-methyl-4-nitropyrrole-2-carboxylate (10). A solution of benzyl alcohol (597mg, 5.52mmol) in THF (3ml) was added to a suspension of NaH (60% in oil, 15mg, 0.38mmol) in THF (1ml) at 0°C. To the resultant clear solution, a solution of 5 (1g, 3.68mmol) in THF (6ml) was added at 0°C and then the mixture was warmed up to room temperature, and stirred for 45min. After addition of $TsOH \cdot H_2O$ (72mg, 0.38mmol), the solvent was removed in vacuo and the residue was purified with column chromatography to give the ester 10 (938mg, 98% yield) as pale yellow plates; mp 112-113°C. Ir($CHCl_3$) 1715, 1500, 1310cm^{-1}. Nmr($CDCl_3$) δ 3.99(3H,s), 5.30(2H,s), 7.40(5H,m), 7.46(1H,d,J=2.0), 7.60(1H,d, J=2.0)ppm. Anal. Calcd for $C_{13}H_{12}N_2O_4$(%): C,60.00; H,4.65; N,10.76. Found: C,59.85; H,4.60; N,10.67.

2-Trimethylsilylethyl 1-methyl-4-nitropyrrole-2-carboxylate (11). A solution of 2-trimethylsilylethyl alcohol (250mg, 2.11mmol) in THF (10ml) was added to a suspension of NaH (54mg, 2.25mmol) in THF (3ml) at 0°C. To the solution, a solution of 5 (500mg, 1.84mmol) in THF (5ml) was added and stirred at 0°C for 5 min. After addition of $TsOH \cdot H_2O$ (455mg, 2.39mmol), the solvent was removed in vacuo and the residue was purified by column chromatography to give the ester 11 (412mg, 83% yield) as colorless plates; mp 81-82°C. Ir($CHCl_3$) 3130, 1710, 1315cm^{-1}. Nmr($CDCl_3$) δ 0.09(9H,s), 1.10(2H, t,J=8.5), 3.99(3H,s),4.36(2H,t,J=8.5), 7.40(1H,d,J=2.2), 7.59(1H,d,J=2.2)ppm. Anal. Calcd for $C_{11}H_{18}N_2O_4Si$(%): C,48.87; H,6.71; N,10.36. Found: C,48.78; H,6.85; N,10.34.

1-Methyl-4-nitropyrrole-2-carboxamidopropionitrile (12). A solution of 3-aminopropionitrile (10g, 143mmol) in THF (15ml) was added dropwise to a stirred solution of 5 (35g, 129mmol) at 0°C. The

reaction mixture was warmed up to room temperature and stirring was continued for 1h. The solvent was removed in vacuo and the residual solid was recrystallized from EtOH to give pale yellow needles of 12 (25.128g, 88% yield). From the mother liquor, additional 12 (2.922g, 10% yield) was obtained by purification with column chromatography; mp 133-134°C (lit.[1b] mp 135°C).

3-(1-Methyl-4-nitropyrrole-2-carboxamido)dimethylaminopropane (13). By the same procedure as that described for 12, 13 was obtained from 5 (27.150g, 100mmol) and 3-dimethylaminopropylamine (12.300g, 120mmol) as pale yellow needles. Yield, 25.155g (99%); mp 129-130°C (lit.[19] mp 126-127°C). Ir ($CHCl_3$) 1655, 1310cm^{-1}. Nmr($CDCl_3$) δ 1.71(2H,m), 2.30(6H,s), 2.48(2H,t,J=5.5), 3.46(2H,q,J=5.5), 3.98(3H,s), 6.90(1H,d,J=2.0), 7.51(1H,d,J=2.0), 8.58(1H,br.)ppm. Anal. Calcd for $C_{11}H_{18}N_4O_3$(%): C,51.96; H,7.13; N,22.03. Found: C,51.66; H,7.21; N,22.00.

1-Methyl-4-nitropyrrole-2-carboxanilide (14). A stirred solution of aniline (1.431g, 15.4mmol) in THF (50ml) at -78°C was treated with 10ml (16.3mmol) of 1.63M solution of n-BuLi in n-hexane, and subsequently a solution of 5 (4.17g, 15.4mmol) in THF (20ml) was added dropwise. The reaction mixture was warmed up to room temperature and stirring was continued for 1h. The mixture was poured into ice water and extracted with AcOEt. The extract was washed with dil.HCl, aqueous $NaHCO_3$, and brine successively, then dried, filtered, and concentrated. The residual solid was recrystallized from $CHCl_3$ to give pale yellow needles. Yield, 1.633g (43%). From the mother liquor, additional 14 (460mg, 12% yield) was obtained by purification with column chromatography on silica gel; mp 213-214°C. Ir($CHCl_3$) 1675, 1520, 1315cm^{-1}. Nmr(DMSO-d_6) δ 4.03(3H,s), 7.10(1H,t,J=7.3), 7.32(2H,t,J=7.3), 7.71(4H,m), 9.79(1H,br.)ppm. Anal. Calcd for $C_{12}H_{11}N_3O_3$(%): C,58.77; H,4.52; N,17.13. Found: C,58.82; H,4.44; N,17.09.

2',5'-Dimethoxy-1-methyl-4-nitropyrrole-2-carboxanilide (15). A solution of 2,5-dimethoxyaniline (3g, 19.6mmol) in THF (15ml) was added to a suspension of NaH (480mg, 20mmol) in THF (5ml) at 0°C. To the resultant solution, a solution of 5 (5.320g, 19.6mmol) in THF (15ml) was added. The mixture was warmed up to room temperature, stirring was continued for 10min, and then extracted with AcOEt. The extract was washed with brine, then dried, filtered, and concentrated. The residue was chromatographed on silica gel to give a yellow powder. Yield, 3.780g (63%); mp 191-192°C. Ir($CHCl_3$) 1675, 1525, 1310cm^{-1}. Nmr(DMSO-d_6) δ 3.78, 3.89, 4.03(3X3H,s), 6.63(1H,dd,J=2.9, 9.0), 6.87(1H,d,J=9.0), 7.37(1H,d,J=1.7), 7.81(2H,m), 8.66(1H,br.)ppm. Anal. Calcd for $C_{14}H_{15}N_3O_5$(%): C,55.08; H,4.95; N,13.76. Found: C,54.95; H,4.91; N,13.61.

1-Methyl-4-(1-methyl-4-nitropyrrole-2-carboxamido)pyrrole-2-carboxamidopropionitrile (16). A suspension of 10% Pd-C (1g) in a solution of 12 (4.061g, 18.3mmol) in MeOH (40ml) was stirred for 2 h under a current of H_2 at room temperature, then filtered. The residual catalyst was washed thoroughly with MeOH and the combined filtrate and washings were concentrated in vacuo to give the crude amino compound. To a solution of this amine in DMF (9ml), 5 (5g, 18.4mmol) was added. There was

spontaneous temperature rize within 20min. Upon cooling to room temperature, part of the product crystallized out of the solution. The solid was dissolved by adding EtOH (150ml) and heating. After cooling to 0°C, the resultant yellow precipitate was collected and washed with cold EtOH to give 16 (5.635g, 90% yield). mp 244-245°C (lit.[12b] mp 254-255°C).

1-Methyl-4-[1-methyl-4-(1-methyl-4-nitropyrrole-2-carboxamido)pyrrole-2-carboxamido]pyrrole-2-carboxamidopropionitrile (17). A suspension of 10% Pd-C (300mg) in a solution of 16 (900mg, 2.6 mmol) in DMF (15ml) and MeOH (15ml) was stirred for 12h under a current of H_2 at room temperature. The catalyst was removed by filtration, then the solvents removed in vacuo. The residual crude amino compound was acylated with 5 (710mg, 2.62mmol) by the same procedure as that described for 16 to give 17 (901mg, 74% yield); mp 263-264°C (lit.[12b] mp 282-285°C).

3-[1-Methyl-4-(1-methyl-4-nitropyrrole-2-carboxamido)pyrrole-2-carboxamido]dimethylaminopropane (18). A solution of 13 (22.750g, 89mmol) in MeOH (150ml) was hydrogenated at atmospheric pressure over PtO_2 (200mg) for 3h. The catalyst was removed by filtration and then the solvent was removed in vacuo. The residual solid was dissolved in DMF (20ml) and concentrated to the half of its original volume under reduced pressure to remove MeOH completely. A solution of 5 (24.289g, 89mmol) in DMF (15ml) was added with stirring at 0°C. The temperature was allowed to rize to ambient temperature. The solvent was removed in vacuo, and the residue was treated with i-PrOH. The resultant crystalline solid was collected and washed with i-PrOH to give 18 (21.250g, 63% yield). The filtrate was concentrated, and the residue was purified by column chromatography on silica gel with 3% conc. NH_4OH in MeOH as a eluent to give additional 18 (8.015g, 24% yield); mp 190-191°C (lit.[19] mp 191-194°C). Ir(KBr) 1665, 1625, 1535, 1310cm^{-1}. Nmr(DMSO-d_6) 1.65(2H,q,J=7.0), 2.13(6H,s), 2.24(2H,t, J=7.0), 3.18(2H,m), 3.81, 3.95(2X3H,s), 6.80(1H,d,J=2.0), 7.20(1H,d,J=2.0), 7.58(1H,d,J=2.0), 8.10(1H, br.), 8.16(1H,d,J=2.0), 10.25(1H,br.)ppm. Anal. Calcd for $C_{17}H_{24}N_6O_4$(%): C,54.24; H,6.43; N,22.33. Found: C,54.10; H,6.43; N,22.07.

3-{1-Methyl-4-[1-methyl-4-(1-methyl-4-nitropyrrole-2-carboxamido)pyrrole-2-carboxamido]pyrrole-2-carboxamido}dimethylaminopropane (19). By the same procedure as that described for 18, 19 was obtained from 18 (14.600g, 39mmol), PtO_2 (100mg), and 5 (11.583g, 43mmol) as a microcrystalline solid. Yield, 15.337g (79%); mp 136-137°C (lit.[19] mp 203-205°C). Ir(KBr) 1645, 1535, 1310cm^{-1}. Nmr(DMSO-d_6) δ 1.70(2H,q,J=7.0), 2.21(6H,s), 2.36(2H,t,J=7.0), 3.40(2H,m), 3.74, 3.83, 3.95(3X3H,s), 6.42(1H,d,J=2.0), 6.50(1H,d,J=2.0), 7.05(1H,d,J=2.0), 7.25(1H,d,J=2.0), 7.53(2H,m), 7.75(2H,br.), 9.38(1H,br.)ppm. Anal. Calcd for $C_{23}H_{30}N_8O_5 \cdot H_2O$(%): C,53.48; H,6.24; N,21.69. Found: C,53.76; H,6.00; N,21.70.

REFERENCES

1. (a) A. C. Finley, F. A. Hochstein, B. A. Sobin, and F. X. Murphy, J. Am. Chem. Soc., 1951, 73,

341; (b) M. M. Julia and N. Préau-Joseph, Compt. Rend. Acad. Sci., 1963, 257, 1115.

2. F. Arcamone, S. Penco, P. R. Orezzi, V. Nicolella, and A. Pirelli, Nature, 1964, 203, 1064; F. Arcamone, P. G. Orezzi, W.Barbieri, V. Nicolella, and S. Penco, Gazz. Chim. Ital., 1967, 97, 1097.
3. For a review, see: C. Zimmer and U. Wähnert, Prog. Biophys. Molec. Biol., 1986, 47, 31.
4. M. Coll, C. A. Frederick, A. H. J. Wang, and A. Rich, Proc. Natl. Acad. Sci. USA, 1987, 84, 8385.
5. D. Goodsell and R. E. Dickerson, J. Med. Chem., 1986, 29, 727; L. A. Marky and K. J. Breslauer, Proc. Natl. Acad. Sci. USA, 1987, 84, 4359; D. Dasgupta, P. Parrack, and V. Sasisekharan, Biochemistry, 1987, 26, 6381; M. Lee, D. K. Chang, J. A. Hartley, P. T. Pon, K. Krowicki, and J. W. Lown, ibid., 1988, 27, 445; B. Ward, R. Rehfuss, J. Goodisman, and J. C. Dabrowiak, ibid., 1988, 27, 1198.
6. For a review, see: P. B. Dervan, Science, 1986, 232, 464.
7. J. H. Griffin and P. B. Dervan, J. Am. Chem. Soc., 1986, 108, 5008; W. S. Wade and P. B. Dervan, ibid., 1987, 109, 1574; J. H. Griffin and P. B. Dervan, ibid., 1987, 109, 6840; R. S. Youngquist and P. B. Dervan, ibid., 1987, 109, 7564.
8. M. L. Kopka, C. Yoon, D. Goodsell, P. Pjura, and R. E. Dickerson, Proc. Natl. Acad. Sci. USA, 1985, 82, 1376.
9. (a) J. W. Lown, K. Krowicki, and G. Bhat, Biochemistry, 1986, 25, 7408; (b) K. Krowicki and J. W. Lown, J. Org. Chem., 1987, 52, 3493.
10. J. W. Lown, K. Krowicki, J. Balzarini, and E. D. Clercq, J. Med. Chem., 1986, 29, 1210, and references cited there.
11. (a) M. Bialer, B. Yagen, and P. Mechoulam, Tetrahedron, 1978, 34, 2389; (b) L. Grehn and U. Ragnarsson, J. Org. Chem., 1981, 46, 3492; (c) J. W. Lown and K. Krowicki, ibid., 1985, 50, 3774.
12. (a) M. J. Weiss, J. S. Webb, and J. M. Smith,Jr., J. Am. Chem. Soc., 1957, 79, 1266; (b) S. Penco, S. Redaelli, and F. Arcamone, Gazz. Chim. Ital., 1967, 97, 1110.
13. S. L. Grokhovskii, A. L. Zhuze, B. P. Gottikh, Bioorg. Khim., 1975, 1, 1616.
14. P. Barker, P. Gendler, and H. Rapoport, J. Org. Chem., 1978, 43, 4849.
15. P. Bélanger, Tetrahedron Letters, 1979, 2505.
16. E. Regel and K. H. Büchel, Ann., 1977, 145.
17. (a) A. Treibs and F. H. Kreuzer, Ann., 1969, 721, 105; (b) J. W. Harbuck and H. Rapoport, J. Org. Chem., 1972, 37, 3618; (c) D. M. Bailey and R. E. Johnson, J. Med. Chem., 1973, 16, 1300.
18. M. Bialer, B. Yagen, R. Mechoulam, J. Med. Chem., 1979, 22, 1296; K. Krowicki, J. Balzarini, E. D. Clercq, R. A. Newman, and J. W. Lown, J. Med. Chem., 1988, 31, 341.
19. E. N. Glibin, B. V. Tsukerman, and O. F. Ginzburg, Zh. Org. Khim., 1977, 13, 2231.

Received, 23rd April, 1988