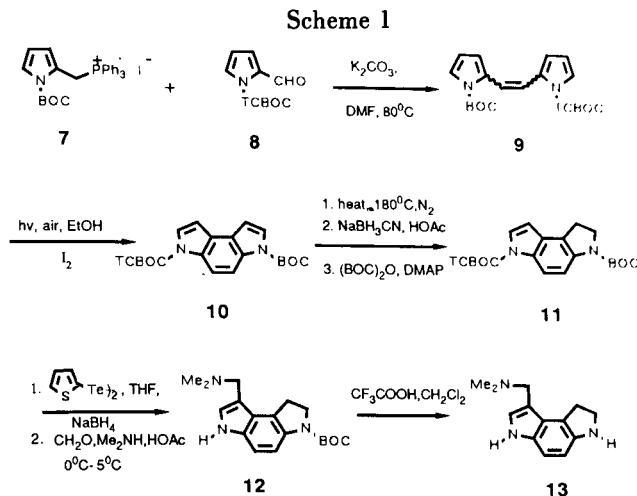




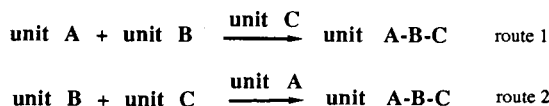
We now report the synthesis of the peptides **5** and **6**. These represent structural modifications of the active analogs **3** and **2** in which the dienone A-unit has been replaced by the tricyclic achiral gramine unit **4**. We reasoned that these new analogs would serve as excellent probes to determine whether or not a gramine-type A-unit would have sufficient alkylating properties to retain good biological activity.

### Synthesis of Analog **5**.

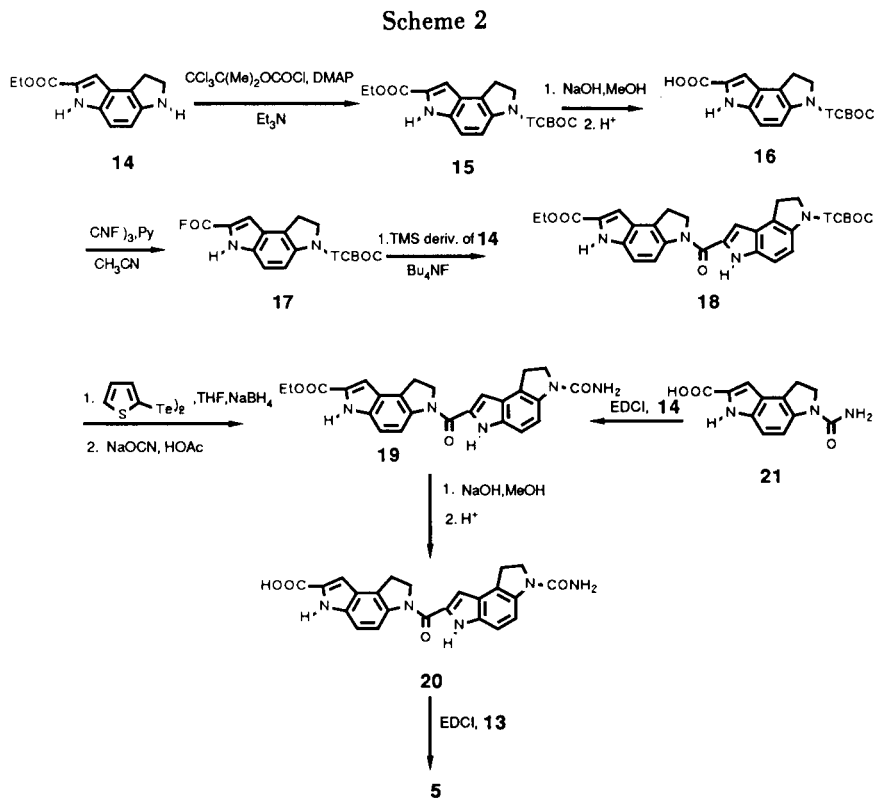
We employed our photochemical strategy [3a] for the construction of the tricyclic unit according to Scheme 1. Wittig reaction of the aldehyde **8** with the phosphonium salt [3f] **7** in the presence of a mild base (potassium carbonate) gave the *cis*- and *trans*-olefins **9** in the ratio of 1:3 (84%). Air-mediated photocyclization of the product **9** as a *cis*-, *trans*-mixture gave the tricyclic system **10** (75%). Thermal deprotection of the *t*-butyloxycarbonyl group [3c] followed by the reduction of the unprotected indole to an indoline using sodium cyanoborohydride and reprotection of the indoline nitrogen using di-*t*-butyl dicarbonate gave compound **11** in an overall yield of 84%. Removal of the 1,1,1-trichloro-2,2-dimethylethoxy carbonyl group by a tellurium based procedure [3d] and reaction of the deprotected indole with formaldehyde-dimethylamine in the presence of acetic acid at 0-5° gave the protected left-hand segment **12** of the analog **5** (79%). Compound **13** was prepared by the action of trifluoroacetic acid on **12** just before the coupling reaction with **20**.



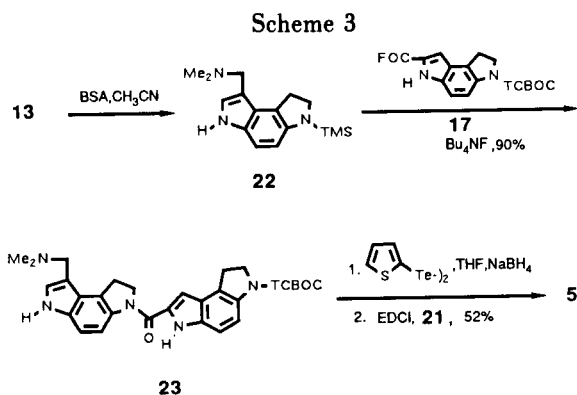
The formation of the peptide bonds could be achieved in two different way with A-, B-, C-units *viz.* by route (1) or route (2) (refer to structure **5**).



Compound **5** was prepared using both routes.



The B-C unit of **5** was prepared as the urea acid **20** according to Scheme 2. Compound **14**, prepared as previously described [3f], was converted to the 1,1,1-trichloro-2,2-dimethylethoxy carbonyl derivatives **15** (84%). Hydrolysis of the ester group of **15** gave **16** (97%) which when reacted with cyanuric fluoride and pyridine by the method of Olah [9] gave the stable acid fluoride **17** (97%). Reaction of the acid fluoride **17** with the trimethylsilyl derivative of **14** gave the peptide **18** (89%) [10]. Deprotection of the 1,1,1-trichloro-2,2-dimethylethoxy carbonyl group failed using the original catalytic tellurolate procedure [3d] due to the insolubility of **18**, but succeeded using a stoichiometric tellurolate modification (Method A). The resulting crude indoline was reacted with aqueous sodium cyanate/acetic acid to give the urea **19** (52%). Hydrolysis of **19** with methanolic sodium hydroxide gave the free acid **20** [3i] (88%). Coupling of this acid with the free indoline **13** in the presence of EDCI [15] gave **5** in 60% yield. Alternatively the dipeptide urea **19** could be obtained by reacting the acid [3f] **21** with the free indoline **14** in the presence of EDCI (Method B). Thus, compound **5** could be obtained by this method (Method B) in an overall yield of 48% from **21** and **14**. An alternative and more direct preparation of **5** was summarized in Scheme 3 which follows route (1) *viz.*,

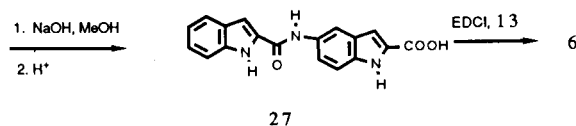
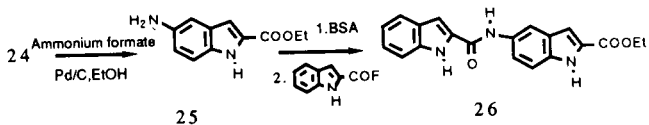


By this method, compound **5** was prepared in an overall yield of 49% starting from **12** and **14**.

#### Synthesis of **6**.

Compound **6** was prepared using both the coupling methodologies [fluoride coupling methodology [10] and using a water soluble peptide coupling agent (EDCI)] according to Scheme 4. The overall yield of **6** starting from the indole-2-carboxylic acid and ethyl 5-nitroindole-2-carboxylate **24** was 42%.

#### Scheme 4



#### Biological Activity.

Both compounds **5** and **6** were sent for biological testing to the Upjohn Company [16] with the following results:

The concentration of the drug required to inhibit by 50% ( $ID_{50}$ ) the growth of the murine L1210 cells in a 3 day *in vitro* assay for **5** was  $2.8 \times 10^{-3}$  mg/ml, whereas for CC-1065 the  $ID_{50}$  was  $3 \times 10^{-5}$  mg/ml, indicating that **5** is several orders of magnitude less potent than CC-1065. In the same *in vitro* assay for compound **6**, the  $ID_{50}$  was 2.3 mg/ml, in contrast to the  $ID_{50}$  of **2** which was  $3.5 \times 10^{-6}$  mg/ml. The situation is very similar *in vivo*. Compound **5** was tested side by side with CC-1065 *in vivo* in P388 leukemic mice with the standard NCI protocol with both the tumor and the drug (which was dosed on days 1, 5, and 9) being administered intraperitoneally. The percent increase in the life span of treated mice over that of control tumored mice (% T/C) at the optimal dose of 3 mg/kg of **5** was 30, whereas in was 65 for CC-1065 at an optimal dose of 0.05 mg/kg. These show that **5** was not only less potent than CC-1065 but was also "significantly less active". At the highest dose tested, 12 mg/kg of **5**, no marked toxicity to the mice was seen but the activity was only marginal with a % T/C of 12.5. At doses below 3 mg/kg (from 0.05 mg/kg up to 1.5 mg/kg) no activity was observed. Observations by Dr. P. Aristoff [16] indicate that tetra-desoxy CC-1065 behaves biologically almost identically as CC-1065. Therefore, the loss of activity and potency with the gramine analog **5** is almost certainly due to the left-hand (*i.e.*, gramine) segment. Compound **6** was tested *in vivo* in P388 leukemic mice with the tumor administered intraperitoneally and the drug dosed intraperitoneally on days 1, 5, and 9. In this experiment, **6** was tested at 6 dose levels between 0.28 mg/kg to 9 mg/kg. No drug toxicity was noted as evidenced by weight loss or premature death of the mice even at the top dose (9 mg/kg). At the top dose only a 5% increase in the lifespan of the mice over controls was observed. The maximum increase in the lifespan of 15% was observed at a dose of 4.5 mg/kg; however, only increases in lifespan of 25% or greater are considered significant in P388. In contrast, in the same experiment **2** at 6 mg/kg produced a 105% increase in life span of mice with 2/6 mice still alive at day 30 (and thus presumably cured). When the induced circular dichroism spectrum (ICD) of the compound **5** was measured in the presence of calf thymus DNA (which is an indication of how well the compound interacts with DNA), a value of 50,000 was obtained for the molar ellipticity ( $\Delta[\Phi]$ ) after 24 hours indicating an interaction of **5** with the DNA. This was still

significantly less than that of CC-1065, **1**, which has a  $\Delta[\Phi]$  of 280,000.

Therefore, one must conclude that the substitution of the left hand A-unit in the CC-1065 analog series with a gramine unit leads to a marked (> 1000 fold) decrease in potency.

## EXPERIMENTAL

### General Data.

Proton nuclear magnetic resonance spectra ( $^1\text{H}$  nmr) were recorded on a Nicolet 200 NMR spectrometer and chemical shifts are reported in  $\delta$  values relative to internal standard tetramethylsilane. The following abbreviations are used in reporting the nmr: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; J, coupling constant. Infrared spectra (ir) were recorded on a Perkin Elmer 781 infrared spectrophotometer as potassium bromide pellets for solids or films for liquids and are uncorrected. Ultra violet (uv) spectra were recorded on a Perkin Elmer Lambda 48 uv/vis spectrophotometer using ethanol as solvent. Electron impact mass spectra (EIMS) were recorded on a Hewlett-Packard 5085A GC/MS system. High resolution mass spectra (HRMS) were recorded at the mass spectrometry facility at MIT. These are fast atom bombardment MS (FABMS) using glycerol/3-nitrobenzyl alcohol (3-NO<sub>2</sub>Ba) as matrices. Melting points (mp) were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Microanalytical data were obtained through Atlantic Microlab, Atlanta, Georgia. Unless indicated otherwise, all reactions were performed in a flame-dried flask using dry distilled solvents maintained under a positive pressure of nitrogen in a balloon. Tetrahydrofuran was distilled from sodium-benzophenone ketyl. Other distilled solvents were stored over either 3A°/4A° molecular sieves. Solvents used for extraction and chromatography were reagent grade. Reactions were heated in silicone oil baths, the stated reaction temperature being the temperature of the bath, within  $\pm 5^\circ$ . Column chromatography was performed by using Merck silica gel (230-400 mesh). Photolysis was performed in a water-cooled quartz or borosilicate immersion well available from Ace Glass Co. The uv source was a Hanovia 450-W, medium pressure mercury vapour lamp which was used with a Pyrex filter. Photolyses were carried out in a specially constructed Pyrex two-walled glass vessel using spectro grade acetonitrile as solvent. In the text, "washed" means washing the organic layer with water unless specified otherwise, "dried" means drying over anhydrous sodium sulfate unless specified otherwise.

1-(1',1',1'-Trichloro-2',2'-dimethylethoxy)carbonyl-2-formylpyrrole (**8**).

A mixture of pyrrole-2-aldehyde [**12**] (3.006 g, 31.6 mmoles), 1,1,2-trichloro-2,2-dimethylethoxy carbonyl chloride (10.08 g, 42 mmoles), triethyl amine (5.76 ml, 42 mmoles), and 4-(dimethylamino)pyridine (300 mg) in acetonitrile (75 ml) was stirred at rt in an atmosphere of nitrogen for 16 hours. The acetonitrile was removed *in vacuo* and the residue was taken up in water and extracted with methylene chloride (3  $\times$  50 ml). The organic layer was washed, dried, and evaporated to yield **8** as a white crystalline solid (8.75 g, 93%), mp 259° (hexane/ethyl acetate);  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  2.09 (6H, s, -Me  $\times$  2), 6.33 (1H, t, ArH), 7.24 (1H, m, ArH), 7.49 (1H, m, ArH), 10.40 (1H, s, CHO); ms: (EIMS)  $m/z$  299, 297 ( $M^+$ ,  $^{37}\text{Cl}$ ,  $^{35}\text{Cl}$ ), 161, 159, 138, 125, 123, 112,

95.

*Anal.* Calcd. for C<sub>10</sub>H<sub>10</sub>Cl<sub>3</sub>NO<sub>2</sub>: C, 40.23; H, 3.38; N, 4.69; Cl, 35.62. Found: C, 40.29; H, 3.39; N, 4.66; Cl, 35.55.

5-[2-[1-[(1,1-Dimethylethyl)oxy]carbonyl]-1H-pyrrol-2-yl]ethenyl]-2-(1',1',1'-trichloro-2',2'-dimethylethyl)oxy]carbonyl-1H-pyrrole (**9**).

To a flask fitted with a magnetic stirbar were added aldehyde **8** (8.02, g, 26.86 mmoles), phosphonium salt [3f] **7** (15.28 g, 26.85 mmoles), anhydrous potassium carbonate (20 g), and dimethyl formamide (200 ml). The stirred reaction mixture was vacuum purged with nitrogen (3x) and then heated on an oil bath for 8 hours at 80°. The cooled reaction mixture was diluted with water (500 ml) and ether (200 ml), stirred vigorously for 30 minutes, and then filtered through a pad of celite. The organic phase was separated and the aqueous phase was extracted with ether (2  $\times$  100 ml). The combined organic phase was washed (brine, 25 ml), dried, and concentrated under reduced pressure. Purification of this residue by chromatography using hexane-ethyl acetate (9:1) as solvent afforded the product, a mixture of *cis*- and *trans*-isomers of **9** (1:3), as a gummy, pale yellow solid (10.41 g; 84%) from which the *trans*-isomer was separated by crystallization from ethanol affording an analytically pure sample as white fibrous needles, mp 149-150°;  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  1.60 (9H, s, -C(Me)<sub>3</sub>), 2.05 (6H, s, =CMe<sub>2</sub>), 6.11-7.57 (8H, m, ArH); ir:  $\nu$  1730, 1690 cm<sup>-1</sup>; ms: (EIMS)  $m/z$  460, 462 ( $M^+$ ,  $^{37}\text{Cl}$ ,  $^{35}\text{Cl}$ ), 404, 406, 360, 362, 246, 202, 157, 57; uv:  $\lambda$  nm (log  $\epsilon$ ): 337 (3.81), 232 (3.80), 205 (3.78).

*Anal.* Calcd. for C<sub>20</sub>H<sub>23</sub>Cl<sub>3</sub>N<sub>2</sub>O<sub>4</sub>·H<sub>2</sub>O: C, 50.07; H, 5.25; N, 5.84. Found: C, 50.27; H, 4.85; N, 5.83.

3-[(1,1-Dimethylethyl)oxy]carbonyl-3H-pyrrolo-[3,2-*e*]-6-[(1',1',1'-trichloro-2',2'-dimethylethyl)oxy]carbonylindole (**10**).

To an ethanolic solution of **9** (2 g in 450 ml) was added a catalytic amount of iodine (50 mg) and irradiated with the uv lamp maintaining a slow and constant stream of air. The disappearance of the starting material was monitored by tlc. After 1 hour and 30 minutes, the solvent was evaporated *in vacuo*. The residue was taken up in methylene chloride and washed with a solution of sodium bisulfite followed by water. The organic layer was dried and evaporated to yield a honey-colored foam (1.91 g) from which a tan-colored solid **10** (1.5 g, 75%) could be obtained by flash column chromatography using hexane-methylene chloride (2:1); mp 145-146° (ethanol);  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  1.71 (9H, s, -CMe<sub>3</sub>), 2.15 (6H, s, =CMe<sub>2</sub>), 6.82 (2H, m, J = 2.8 Hz, ArH), 7.71, 7.68 (2H, d, J = 3.49 Hz, ArH), 8.24 (2H, ArH); ir:  $\nu$  1730, 1690, 1580 cm<sup>-1</sup>; ms: (EIMS)  $m/z$  460, 458 ( $M^+$ ,  $^{37}\text{Cl}$ ,  $^{35}\text{Cl}$ ), 404, 402, 360, 358, 244, 200, 155, 57; uv: [ $\lambda$  nm (log  $\epsilon$ ): 325 (3.30), 301 (3.60), 290 (3.70), 282 (3.78), 250 (3.70), 202 (3.68).

*Anal.* Calcd. for C<sub>20</sub>H<sub>21</sub>Cl<sub>3</sub>N<sub>2</sub>O<sub>4</sub>: C, 52.25; H, 4.60; N, 6.095. Found: C, 52.13; H, 4.60; N, 6.06.

3-[(1,1-Dimethylethyl)oxy]carbonyl-1,2-dihydro-3H-pyrrolo-[3,2-*e*]-6-[(1',1',1'-trichloro-2',2'-dimethylethyl)oxy]carbonyl indole (**11**).

Compound **10** (1 g) was heated in a round bottom flask under a positive pressure of nitrogen at 180°. At 145° the solid started melting gave out small bubbles of carbon dioxide, and turned green. When the evolution of carbon dioxide ceased, the greenish gum was cooled and purified by flash column chromatography on silica gel using methylene chloride as the eluting solvent to give a greyish white solid of **10a** (681 mg, 87%) mp 185° (methanol);  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  2.12 (6H, s, =CMe<sub>2</sub>),

6.46 (2H, ArH), 7.66, 6.86 (2H, q, J = 3.7 Hz, ArH), 7.36 (1H, d, J = 7.06 Hz, ArH), 8.18 (1H, d, J = 9 Hz, ArH); ms: (EIMS) *m/z* 360, 358 (M<sup>+</sup>, <sup>37</sup>Cl, <sup>35</sup>Cl), 200, 183, 155.

*Anal.* Calcd. for C<sub>15</sub>H<sub>13</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>2</sub>: C, 49.82; H, 4.18; N, 7.75. Found: C, 50.37; H, 3.81; N, 7.62.

This compound was used in the next step without further purification. To this solid **10a** (681 mg) in glacial acetic acid (20 ml) was added sodium cyanoborohydride (300 mg) in small portions at 15 minute intervals maintaining the temperature at 15-20°. After 2 hours at 20°, the acetic acid was removed *in vacuo*; water was added to the residue and was repeatedly extracted with methylene chloride (3 × 50 ml). The organic layer was washed, dried, and evaporated to yield the indoline as a greyish white solid (650 mg), mp 158°; <sup>1</sup>H nmr (deuteriochloroform): δ 2.09 (6H, s, =CMe<sub>2</sub>), 3.18 (2H, t, J = 7.5 Hz, -CH<sub>2</sub>), 3.65 (2H, t, J = 7.5 Hz, -CH<sub>2</sub>), 6.42, 7.56 (2H, q, J = 3.74 Hz, ArH), 6.74, 7.94 (2H, q, J = 9 Hz, ArH); to this solid (650 mg) in acetonitrile (10 ml) was added di-*t*-butyl dicarbonate (300 mg) and a catalytic amount of 4-(dimethylamino)pyridine (25 mg). The whole solution was purged with nitrogen and was stirred at rt for 16 hours. Evaporation of acetonitrile followed by the addition of water (50 ml) and extracting the aqueous layer with methylene chloride yielded a gummy solid which could be purified further by column chromatography on silica gel using methylene chloride-hexane (1:2) as the eluting solvent to yield compound **11** as a white microcrystalline solid (850 mg, overall yield from 1 g of **10** is 84%), mp 172° (hexane). <sup>1</sup>H nmr (deuteriochloroform): δ 1.55 (9H, s, C-Me<sub>3</sub>), 2.11 (6H, s, -CMe<sub>2</sub>), 3.23 (2H, t, J = 8 Hz, -CH<sub>2</sub>), 4.11 (2H, t, J = 8 Hz, -CH<sub>2</sub>), 7.26 (1H, ArH), 7.60, 6.46 (2H, q, J = 4 Hz, ArH), 8.03 (1H, ArH); ms: (EIMS) *m/z* 464, 462 (M<sup>+</sup>, <sup>37</sup>Cl, <sup>35</sup>Cl), 406, 404, 362, 360, 246, 202, 201, 157, 156, 130, 57; ir: ν 2970, 2905, 2840, 1730, 1690, 1590 cm<sup>-1</sup>; uv: λ nm (log ε) 317 (3.65), 265 (3.92), 240 (3.88).

*Anal.* Calcd. for C<sub>20</sub>H<sub>23</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>4</sub>: C, 52.02; H, 5.02; N, 6.07. Found: C, 52.09; H, 5.06; N, 6.05.

3-[(1,1-Dimethylethyl)oxy]carbonyl-1,2-dihydro-3*H*-pyrrolo-[3,2-*e*]-8-(*N,N*-dimethylamino methyl)indole (**12**).

Compound **11** (1 g, 2.17 mmoles) and 2,2-bis-thienyl ditelluride (292 mg, 0.69 mmole) in tetrahydrofuran (100 ml) were heated under reflux in an atmosphere of nitrogen. To this hot solution was added a solution of sodium borohydride (392 mg, 8.7 mmoles in 33 ml water, stabilized with 4 drops of 40% sodium hydroxide) in "small aliquots". The red color of the solution disappeared as soon as the solution of sodium borohydride was added and reappeared after a few minutes. The solution of sodium borohydride was added again. This process was repeated until the red color did not reappear (this took nearly 40 minutes). After checking the tlc (silica gel GF<sub>254</sub>, hexane-ethyl acetate (4:1)) for the disappearance of the starting material, the reaction mixture was cooled, exposed to air, and acidified with 4*N* hydrochloric acid to pH 6 and was extracted with ethyl acetate (3 × 10 ml). The combined organic layer was washed, dried, and evaporated *in vacuo* to yield a brown colored product which was purified by column chromatography on silica gel using hexane-methylene chloride (1:1) to give **11a** as a white microcrystalline powder (500 mg, 89%), mp 195° (hexane/chloroform); <sup>1</sup>H nmr (deuteriochloroform): δ 1.56 (9H, s, C-Me<sub>3</sub>), 3.25 (2H, t, J = 8.6 Hz, -CH<sub>2</sub>), 4.08 (2H, t, J = 8.6 Hz, -CH<sub>2</sub>), 6.38 (1H, s, ArH), 7.20 (3H, m, ArH), 8.11 (1H, bs, -NH); ms: (EIMS) *m/z* 258 (M<sup>+</sup>), 202 (M-56), 201, 157, 130, 57. To a mixture of formaldehyde (37% aqueous solution; 204.1 ml) and *N,N*-dimethylamine (40% solution in water, 343 ml) cooled in an icebath

at 0-5° was added glacial acetic acid (2 ml) drop by drop. To this mixture at 0° was added the above deprotected amine **11a** (500 mg) in small portions, stirred, and allowed to come to rt. After 16 hours, water was added and the aqueous layer was extracted with ether. The aqueous layer, after the ether wash, was cooled and basified with a saturated solution of sodium carbonate to pH 8 and extracted with ether (3 × 50 ml). The ether layer was washed (brine), dried, and evaporated to yield a white foam of **12** which crystallized nicely from ether (534 mg, 78.5% starting from **11**); mp 164°; <sup>1</sup>H nmr (deuteriochloroform): δ 1.58 (9H, s, -CMe<sub>3</sub>), 2.32 (6H, s, -CH<sub>2</sub>N-Me<sub>2</sub>), 3.46 (2H, t, J = 8.6 Hz, -CH<sub>2</sub>), 3.63 (2H, s, -CH<sub>2</sub> NMe<sub>2</sub>), 4.08 (2H, t, J = 8.4 Hz, -CH<sub>2</sub>), 7.17 (3H, m, ArH), 8.21 (1H, bs, -NH); ir: ν 3140, 3100, 1680, 1590 cm<sup>-1</sup>; ms: (EIMS) *m/z* 315 (M<sup>+</sup>), 270, 214, 170, 169, 149, 115, 58, 57.

*Anal.* Calcd. for C<sub>18</sub>H<sub>25</sub>N<sub>3</sub>O<sub>2</sub>: C, 68.54; H, 7.99; N, 13.33. Found: C, 68.60; H, 8.02; N, 13.25.

1,2-Dihydro-8-(dimethylamino)methyl-3*H*-pyrrolo[3,2-*e*]indole (**13**).

To compound **12** (301.5 mg, 0.96 mmole) in methylene chloride (5 ml) at 0-5° was added trifluoroacetic acid (0.5 ml) drop by drop. After 30 minutes the methylene chloride was removed *in vacuo* and the resulting syrup was dried thoroughly *in vacuo* to give the trifluoroacetate salt of **13** (290 mg); <sup>1</sup>H nmr (deuteriochloroform): δ 11.84 (1H, bs, -NH), 11.81 (1H, bm, -NH), 7.91-7.14 (ArH), 4.42 (2H, s, -CH<sub>2</sub>), 3.87, 3.80, 3.69, 3.61 (4H, m, -CH<sub>2</sub> × 2), 2.80 (6H, s, -CH<sub>2</sub>NMe<sub>2</sub>). This trifluoroacetate salt was basified under nitrogen using dilute ammonia (4*N*) and extracted with methylene chloride and dried to give **13** which was used as such for further reaction (kept under nitrogen).

3-[(1',1'-Trichloro-2',2'-dimethylethyl)oxy]carbonyl-1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole-7-carboxylic Acid Ethyl Ester (**15**).

A mixture of indoline **14** [3f] (1.127 g, 4.9 mmoles), 1,1,1-trichloro-2,2-dimethylethylloxycarbonyl chloride (1.32 g, 5 mmoles), triethylamine (760 ml, 5 mmoles), and 4-(dimethylamino)pyridine (55 mg) in acetonitrile (25 ml) was stirred at rt in an atmosphere of nitrogen, for 16 hours. The acetonitrile was removed *in vacuo*. The residue was taken up in water and repeatedly extracted with methylene chloride (3 × 50 ml). The organic layer was washed, dried, and evaporated to yield **15** as a white, fluffy solid (1.78 g, 84%), mp 228° (benzene); <sup>1</sup>H nmr (deuteriochloroform): δ 1.42 (3H, t, J = 7.0 Hz, -CH<sub>2</sub>Me), 2.03 (6H, s, =CMe<sub>2</sub>), 3.30 (2H, t, J = 8.8 Hz, -CH<sub>2</sub>), 4.21 (2H, t, J = 8.8 Hz, -CH<sub>2</sub>), 4.42 (2H, q, J = 7.0 Hz, -CH<sub>2</sub>Me), 7.09 (1H, s, ArH), 7.27, 8.02 (2H, q, J = 8 Hz, ArH × 2), 8.92 (1H, bs, NH); ms: (EIMS) *m/z* 434, 432 (M<sup>+</sup>, <sup>37</sup>Cl, <sup>35</sup>Cl), 368, 274, 272, 256, 228, 184, 156, uv: [λ nm (log ε)] 339 (3.60), 290 (4.01), 297 (4.06), 248 (4.1).

*Anal.* Calcd. for C<sub>18</sub>H<sub>17</sub>Cl<sub>3</sub>N<sub>2</sub>O<sub>4</sub>·½C<sub>6</sub>H<sub>6</sub>: C, 53.35; H, 4.69; N, 5.93. Found: C, 53.37; H, 4.82; N, 5.85.

3-(1',1'-Trichloro-2',2'-dimethylethylloxycarbonyl)-1,2-dihydro-3*H*-pyrrolo-[3,2-*e*]indole-7-carboxylic Acid (**16**).

To a solution of the above ester **15** (1 g, 2.3 mmoles) in methanol (50 ml) was added a solution of sodium hydroxide (500 mg in 10 ml water) and the resulting solution was heated under reflux under nitrogen for 3 hours. The solution was cooled, acidified with concentrated hydrochloric acid to pH 2, and cooled in ice again. The separated white solid **16** was filtered, washed, and dried to yield a white microcrystalline powder (720 mg, 97%); mp 296° (methanol); <sup>1</sup>H nmr (deuteriochloroform + dimethyl sulfox-

ide- $d_6$ ):  $\delta$  2.04 (6H, s,  $-CMe_2$ ), 3.30 (2H, t,  $J = 8$  Hz,  $-CH_2$ ), 4.20 (2H, t,  $J = 8$  Hz,  $CH_2$ ), 7.18 (2H, m,  $ArH$ ), 8.03 (1H, d,  $J = 8$  Hz,  $ArH$ ), 8.85 (1H, bs,  $-NH$ ); ir:  $\nu$  3320, 1715, 1685  $cm^{-1}$ ; ms: (EIMS)  $m/z$  406, 404 ( $M^+$ ,  $^{37}Cl$ ,  $^{35}Cl$ ), 246, 228, 201, 183, 156, 128, 101; HRMS: (FABMS-Glycerol)  $m/z$  405.0175 [calcd. for  $C_{16}H_{14}Cl_3N_2O_4 + H$ ]: 405.0176].

*Anal.* Calcd. for  $C_{16}H_{14}Cl_3N_2O_4 \cdot \frac{1}{4}CH_3OH$ : C, 47.00; H, 4.06; N, 6.64. Found: C, 47.37; H, 4.02; N, 6.61.

3-[[3'-(1'',1'',1''-Trichloro-2'',2''-dimethylethyl)oxy]carbonyl-1',2'-dihydro-3H-pyrrolo[3,2-e]indole-7'-carbonyl]-1,2-dihydro-3H-pyrrolo[3,2-e]indole-7-carboxylic Acid Ester (**18**).

#### 1) Preparation of the Acid Fluoride **17**.

To the above carboxylic acid **16** (400 mg, 0.985 mmole) in acetonitrile (3 ml) was added cyanuric fluoride (66.5 mg, 0.493 mmole) in acetonitrile (1 ml) drop by drop under nitrogen. Immediately, dry pyridine (78 mg, 0.985 mmole) was added drop by drop. The resulting yellow solution was stirred vigorously under nitrogen for 16 hours. Acetonitrile was removed *in vacuo*. The residue was suspended in water and extracted with methylene chloride (3  $\times$  25 ml). The organic layer was washed (ice water), dried, and evaporated to yield a greenish yellow solid **17** (390 mg, 97%), mp 190°;  $^1H$  nmr (deuteriochloroform):  $\delta$  2.03 (6H, s,  $-CMe_2$ ), 3.33 (2H, t,  $J = 8$  Hz,  $-CH_2$ ), 4.23 (2H, t,  $J = 8$  Hz,  $-CH_2$ ), 7.29 (2H, m,  $ArH$ ), 8.12 (1H, d,  $J = 9$  Hz,  $ArH$ ), 8.80 (1H, bs,  $-NH$ ); ir:  $\nu$  3200, 1800 ( $-COF$ ), 1740, 1690  $cm^{-1}$ ; ms: (EIMS)  $m/z$  408, 406 ( $M^+$ ,  $^{37}Cl$ ,  $^{35}Cl$ ), 248, 228, 183, 155. To the trimethylsilyl derivative of **14** [**13**] (70.6 mg, 0.245 mmole) in acetonitrile (10 ml) was added the acid fluoride **17** (100 mg, 0.245 mmole) and tetrabutylammonium fluoride (10 mg). The resulting mixture was stirred at rt under nitrogen for 16 hours. The solid that separated was filtered, washed (ice water), and dried to yield **18** (136 mg, 90%); as a white microcrystalline powder mp 286°, which was crystallized from benzene;  $^1H$  nmr (dimethyl sulfoxide- $d_6$ ):  $\delta$  1.36 (3H, t,  $J = 7$  Hz,  $-Me$ ), 1.96 (6H, s,  $-CMe_2$ ), 4.62, 4.40 (6H, m), 7.01 (1H, s,  $ArH$ ), 7.12 (1H, s,  $ArH$ ), 7.33 (2H, d,  $J = 8.3$  Hz,  $ArH$ ), 7.82 (1H, d,  $J = 8.6$  Hz,  $ArH$ ), 8.29 (1H, d,  $J = 8.3$  Hz,  $ArH$ ), 11.90, 11.71 (1H, each s,  $-NH \times 2$ ); ir:  $\nu$  3200, 3060, 1700, 1600  $cm^{-1}$ ; HRMS: (FABMS-3- $NO_2$ BA)  $m/z$  616.1047 [Calcd. for  $C_{29}H_{27}^{35}Cl_3N_4O_5 + H$ ]: 616.1047],  $m/z$  617.1115 [Calcd. for  $C_{29}H_{27}^{37}Cl_3N_4O_5 + H$ ]: 617.1125].

*Anal.* Calcd. for  $C_{29}H_{27}Cl_3N_4O_5$ : C, 56.48; H, 4.42; N, 9.09. Found: C, 56.50; H, 4.45; N, 9.08.

3-[[3''-(3'-Carbamoyl-1'',2''-dihydro-3H-pyrrolo[3,2-e]indole-7''-carbonyl)-1,2-dihydro-3H-pyrrolo[3,2-e]indole-7''-carboxylic Acid Ester (**19**).

#### Method A.

To the above 1'',1'',1''-trichloro-2'',2''-dimethylethoxy carbonyl derivative **18** (50 mg, 0.083 mmole) in dimethylformamide (5 ml) was added 2,2'-bis-thienyl ditelluride (15 mg) and heated to 100° in an atmosphere of nitrogen. Sodium borohydride (15 mg in 0.5 ml water) was added in drops until the color of the tellurium reagent was permanently discharged (~40 minutes) and the reaction was maintained at this temperature for another 30 minutes. The solvent was removed *in vacuo*. To the residue was added acetic acid (2 ml) and sodium cyanate (50 mg in 0.5 ml water). The reaction mixture was warmed on a water bath for 15 minutes. Water was added to the reaction mixture and extracted with methylene chloride (a large excess). The organic layer was dried and

evaporated *in vacuo* to leave a tan-colored solid which was washed repeatedly with hexane to give **19** as a microcrystalline powder (19.7 mg, 52%), mp 296°;  $^1H$  nmr (dimethyl sulfoxide- $d_6$ ):  $\delta$  1.42 (3H, t,  $J = 7$  Hz,  $-Me$ ), 4.06 (2H, t,  $J = 8.5$  Hz,  $-CH_2$ ), 4.38 (2H, t,  $J = 7$  Hz,  $-CH_2$ ), 4.68 (2H, t,  $J = 8$  Hz,  $-CH_2$ ), 6.01 (bs  $-NH_2$ ), 8.22, 7.99, 7.97, 7.63, 7.40, 7.36, 7.31, 7.09, 6.84, 6.89 (complex m,  $ArH$ ), 11.84, 11.49 (2H, each bs,  $-NH \times 2$ ); ir:  $\nu$  3300, 2900, 1700, 1650, 1610, 1590  $cm^{-1}$ ; HRMS: (FABMS-Glycerol)  $m/z$  458.1862 [Calcd. for  $C_{25}H_{24}N_5O_4 + H$ ]: 458.1828].

#### Method B.

The dideoxy derivative **21** [3f] (69 mg, 0.28 mmole), compound **14** (64.4 mg, 0.28 mmole), and EDCI (114 mg, 0.059 mmole) in tetrahydrofuran (10 ml) were stirred at rt for 18 hours under nitrogen. The solvent was removed *in vacuo*. The residue was suspended in water and acidified with dilute hydrochloric acid to pH 2. A greenish, yellow solid that separated after cooling was filtered, washed (sodium carbonate solution, cold water), and dried (over phosphorus pentoxide), (112 mg, 87.5%), mp 296°, identical with the compound **19** prepared by Method A (ir, mp).

3-[[3''-(3'-Carbamoyl-1'',2''-dihydro-3H-pyrrolo[3,2-e]indole-7''-carbonyl)-1,2-dihydro-3H-pyrrolo[3,2-e]indole-7''-carboxylic Acid (**20**).

Compound **19** (83 mg, 0.18 mmole) in methanol (10 ml), tetrahydrofuran (2 ml), and aqueous sodium hydroxide (4N, 0.24 ml) were heated on an oil bath in an atmosphere of nitrogen under reflux for 90 minutes. Methanol was removed *in vacuo* and the aqueous layer was cooled and acidified to pH 2. The solid that separated on cooling was filtered, washed (ice water), and dried (over phosphorus pentoxide) to give a greyish white powder **20** (714 mg, 92%), mp > 280° [14].

2-[[3''-(3'-Carbamoyl-1'',2''-dihydro-3H-pyrrolo[3,2-e]indole-7''-carbonyl)-1'',2''-dihydro-3H-pyrrolo[3,2-e]indole-7''-carbonyl]-1,2-dihydro-3H-pyrrolo[3,2-e]-8-(*N,N*-dimethylamino methyl)indole (**5**).

The above carboxylic acid **20** (75 mg, 0.174 mmoles), compound **13** (37.54 mg, 0.174 mmoles), and EDCI (94 mg, 0.49 mmoles) in dimethylformamide (3 ml) were stirred at rt for 72 hours. The solvent was completely removed *in vacuo*. The residue was triturated with a cold dilute hydrochloric acid to pH 2. The brown-colored solid that separated after cooling was filtered, washed with a 5% solution of sodium carbonate, then water, and dried. Compound **5**, obtained as a brown colored powder (103.7 mg, 99%), was further purified by passing through a short column of sephadex-LH 20 using methanol-tetrahydrofuran as the eluant to give **5** (62.9 mg, 60%); mp > 350°;  $^1H$  nmr (dimethyl sulfoxide- $d_6$ ):  $\delta$  2.85 (6H, s,  $-CH_2NMe_2$ ), 3.32, 3.97, 4.43, 4.92 (Each m,  $-CH_2$ ), 3.84 (2H, s,  $-CH_2-NMe$ ), 8.89, 8.59, 8.14, 8.11, 7.68, 7.57, 7.34, 7.05 (9H, m,  $ArH$ ), 11.27 (1H, s,  $-NH$ ), 12.01 (2H, m,  $-NH \times 2$ ); ir:  $\nu$  3250, 2900, 2830, 1690, 1650, 1600  $cm^{-1}$ ; ms: (FABMS-3- $NO_2$ BA)  $m/z$  568 (626-58), 523, 412.

3-[[3'-(1'',1'',1''-Trichloro-2'',2''-dimethylethoxy carbonyl)-1'',2''-dihydro-3H-pyrrolo[3,2-e]indole-7''-carbonyl]-1,2-dihydro-3H-pyrrolo[3,2-e]-8-(*N,N*-dimethylamino methyl)indole (**23**).

To the trifluoroacetate salt of **13** (290.0 mg, 0.88 mmole) and triethylamine (0.1 ml) in acetonitrile (5 ml), was added bis-trimethylsilylacetamide (107 ml, 0.53 mmole) in acetonitrile (1 ml) and the mixture was stirred at rt in an atmosphere of nitrogen for 2 hours. The solvent and the excess reagent were removed *in*

*vacuo* to give a gum **22** which was dissolved in acetonitrile (2 ml). To this was added the acid fluoride **17** (390 mg, 0.95 mmole) in acetonitrile (5 ml) followed by tetrabutyl ammonium fluoride (10 mg) and stirred under nitrogen at rt for 16 hours. The solid that separated was filtered, washed with ice water, and dried (over phosphorus pentoxide) to give compound **23** (429 mg, 80%) which was crystallized from ethyl acetate-methanol mp > 300°; <sup>1</sup>H nmr (deuteriochloroform): δ 2.03 (6H, s, -CMe<sub>2</sub>), 2.28 (6H, s, -CH<sub>2</sub>NMe<sub>2</sub>), 3.33 (2H, t, J = 8 Hz, -CH<sub>2</sub>), 3.56 (2H, s, -CH<sub>2</sub>NMe<sub>2</sub>), 3.71 (2H, t, J = 8 Hz, -CH<sub>2</sub>), 4.21 (2H, t, J = 8 Hz, -CH<sub>2</sub>), 4.61 (2H, t, J = 8 Hz, -CH<sub>2</sub>), 6.82 (1H, ArH), 7.46, 7.42, 7.37, 7.34 (3H, ArH), 7.92 (1H, d, J = 9 Hz, ArH), 8.28 (1H, d, J = 8.3 Hz, ArH), 11.03, 10.60 (2H, each bs, -NH × 2); ir: ν 3300, 2940, 1725, 1620, 1580 cm<sup>-1</sup>; HRMS: (FABMS-3NO<sub>2</sub>BA) m/z 602.1494 [Calcd. for C<sub>29</sub>H<sub>31</sub><sup>35</sup>Cl<sub>3</sub>N<sub>5</sub>O<sub>3</sub> + H], 602.1493].

3-[3'-(3'-Carbamoyl-1'-2'-dihydro-3H-pyrrolo[3,2-e]indole-7'-carbonyl)-1",2"-dihydro-3H-pyrrolo[3,2-e]indole-7"-carbonyl]-1,2-dihydro-3H-pyrrolo-[3,2-e]-8-(N,N-dimethylaminomethyl)indole (**5**).

To a solution of **23** (50 mg, 0.08 mmole) and 2,2'-bisthiényl ditelluride (15 mg) in dimethylformamide (5 ml) at 100° under nitrogen was added a solution of sodium borohydride (15 mg in 0.5 ml water and stabilized with a drop of 40% sodium hydroxide) in drops until the red color is discharged permanently (this took ~45 minutes). After 2 hours at this temperature, the solvent was removed *in vacuo* and the residue was extracted with methylene chloride (3 × 15 ml). The organic layer was dried and evaporated *in vacuo*. The residue was repeatedly washed with hexane (3 × 15 ml) to remove any unreacted telluride reagent. To the resulting residue in acetonitrile (5 ml) and dimethyl formamide (3 ml) was added EDCI (75 mg) and the acid **21** (19.6 mg, 0.08 mmole). The mixture was stirred under nitrogen at rt for 16 hours. The solvent was removed *in vacuo* and the solid that separated was filtered, washed with dilute hydrochloric acid followed by a very dilute ammonia, and dried (over phosphorus pentoxide) to yield a pale brown microcrystalline powder **5** (28 mg, 55.9%), mp > 350°, identical with compound **5** prepared earlier from **20** (ir, mp).

#### 5-Aminoindole-2-carboxylic Acid Ethyl Ester (**25**).

To the 5-nitroindole-2-carboxylic acid, ethyl ester [10] **24** (1.5 g, 6.4 mmoles) in ethanol (100 ml) was added ammonium formate (1.612 g, 25.6 mmoles) and palladium on carbon (5%, 150 mg). The mixture was refluxed on an oil bath at 90° for 30 minutes under nitrogen. Palladium on carbon was filtered on a pad of celite and the filtrate was concentrated *in vacuo*. The residue was taken up in water and basified with ammonia to pH 8 and extracted with ether (3 × 50 ml). The ether layer was washed (brine), dried, and evaporated to yield a tan-colored solid which was crystallized from methanol to provide crystals of **25** (1.24 g, 95%) mp 98° [11].

#### 5-(N-2'-Carbonylindolyl)aminoindole-2-carboxylic Acid Ethyl Ester (**26**).

To compound **25** (204 mg, 1 mmole) in acetonitrile (5 ml) was added bis trimethylsilyl acetamide (100 mg, 0.5 mmole) and the reaction mixture was stirred for 1 hour at rt under nitrogen. The solvent and the excess reagent were removed *in vacuo*. To the residue was added acetonitrile (3 ml), indole-2-carbonyl fluoride [10] (161 mg, 1 mmole) and tetrabutylammonium fluoride (10 mg). The mixture was stirred at rt for 18 hours. The solid that

separated was filtered and was crystallized from methanol-methylene chloride to give **26** (300 mg, 86%), mp 282° dec; <sup>1</sup>H nmr (dimethylsulfoxide-d<sub>6</sub>): δ 1.31 (3H, t, J = 7 Hz, -Me), 4.31 (2H, q, J = 7 Hz, -CH<sub>2</sub>Me), 7.66-7.02 (8H, m, ArH), 8.13 (1H, s, ArH), 11.82, 11.66 (2H, each s, -NH), 10.13 (1H, bs, -NH); ir: ν 3305, 3260, 1695, 1640, 1605 cm<sup>-1</sup>; ms: (EIMS) m/z 347 (M<sup>+</sup>), 348, 204, 158, 89.

*Anal.* Calcd. for C<sub>20</sub>H<sub>17</sub>N<sub>3</sub>O<sub>3</sub>·H<sub>2</sub>O: C, 68.75; H, 5.48; N, 12.03. Found: C, 68.88; H, 5.30; N, 11.56.

#### 5-(N-2'-Carbonylindolyl)aminoindole-2-carboxylic Acid (**27**).

To the above ester **26** (250 mg, 0.72 mmoles) in a mixture of tetrahydrofuran-methanol-water (3:2:1, 50 ml) was added sodium hydroxide (240 mg, 6 mmoles). The mixture was refluxed on an oil bath for 30 minutes under nitrogen. The residue, after removing the solvent, was suspended in water and acidified with 4N hydrochloric acid to pH 2 and cooled. The solid that separated was filtered, washed, dried (over phosphorus pentoxide), and crystallized from methanol to give **27** (220 mg, 96%), mp 310° dec; <sup>1</sup>H nmr (dimethyl sulfoxide-d<sub>6</sub>): δ 7.23-7.08 (2H, m, ArH), 7.70-7.40 (5H, ArH), 8.18 (1H, ArH), 9.99 (1H, ArH), 11.49 (2H, bs, exchangeable protons); ms: (EIMS) m/z 319 (M<sup>+</sup>) 275, 176, 158, 144, 132, 116, 89, 73, 57.

*Anal.* Calcd. for C<sub>18</sub>H<sub>13</sub>N<sub>3</sub>O<sub>3</sub>·1/4H<sub>2</sub>O: C, 66.76; H, 4.20; N, 12.98. Found: C, 67.07; H, 4.44; N, 12.98.

3'-[5-(N-2'-Carbonyl indolyl)aminoindole-2-carbonyl]-1",2"-dihydro-3H-pyrrolo-[3,2-e]-7"--(N,N-dimethylaminomethyl)indole (**6**).

To compound **13** (61.15 mg, 0.284 mmole) in acetonitrile (5 ml) was added the above carboxylic acid **27** (91 mg, 0.284 mmole) and EDCI (178 mg, 0.92 mmole). The reaction mixture was allowed to stir at rt under nitrogen for 16 hours. After removing the solvent *in vacuo*, the residue was triturated with dilute hydrochloric acid (4N, 1 ml), cooled, and filtered. The residue, after washing with water followed by dilute ammonia, was crystallized from methanol (72 mg, 61%) to give **6** as a tan-colored solid. This compound was further purified by passing through a short column of sephadex-LH 20 using methanol-tetrahydrofuran as the eluting solvent, mp > 320°; <sup>1</sup>H nmr (dimethyl sulfoxide-d<sub>6</sub>): δ 2.85 (6H, s, -CH<sub>2</sub>NMe<sub>2</sub>), 3.32, 3.97, 4.43, 4.92 (each m, -CH<sub>2</sub>), 3.84 (2H, s, CH<sub>2</sub>NMe<sub>2</sub>), 7.23-7.06 (3H, m, ArH), 7.70-7.40 (7H, ArH), 8.18 (1H, ArH), 9.99 (1H, ArH), 11.49 (2H, bs exchangeable H); ir: ν 3280, 2900, 1670, 1610 cm<sup>-1</sup>; ms: (EIMS) m/z 372 (M-144), 301, 277, 266, 203, 204, 158, 144, 116, 89, 69, 58.

#### Acknowledgements.

We gratefully acknowledge the financial support of the National Institutes of Health (CA 41995). We thank Dr. C. Costello and the Regional Mass Spectrometry Laboratory at MIT for some HRMS and FABMS data (NIH research grant RR00317). We thank the Upjohn Company for the biological testing of the analogs.

#### REFERENCES AND NOTES

- [1] L. J. Hanka, A. Dietz, S. A. Gerpheide, S. L. Kuentzel and D. G. Martin, *J. Antibiot.*, **31**, 1211 (1978); D. G. Martin, C. Biles, S. A. Gerpheide, L. J. Hanka, W. C. Krueger, J. P. McGovern, S. A. Mizaak, G. L. Neil, J. C. Stewart and J. Visser, *ibid.*, **34**, 1119 (1981).
- [2] For a recent review of the chemistry, mechanism of action, and biological properties of CC-1065 see: V. L. Reynolds, J. P. McGovern and H. L. Hurley, *J. Antibiot.*, **31**, 319 (1986). For a review on covalent bonding of CC-1065 to minor grooves of DNA, see: L. H. Hurley and D. R. Needham-VanDevanter, *Acc. Chem. Res.*, **19**, 230 (1986).

- [3] [a] V. H. Rawal and M. P. Cava, *J. Chem. Soc., Chem. Commun.*, 1526 (1984); [b] V. H. Rawal, R. J. Jones and M. P. Cava, *Tetrahedron Letters*, **26**, 2423 (1985); [c] V. H. Rawal and M. P. Cava, *Tetrahedron Letters*, **25**, 6141 (1985); [d] M. V. Lakshmikantham, Y. A. Jackson, R. J. Jones, G. J. O'Malley, K. Ravichandran and M. P. Cava, *Tetrahedron Letters*, **27**, 4687 (1986); [e] V. H. Rawal, R. J. Jones and M. P. Cava, *Heterocycles*, **25**, 701 (1987); [f] V. H. Rawal, R. J. Jones, and M. P. Cava, *J. Org. Chem.*, **52**, 19 (1987); [g] R. E. Bolton, C. J. Moody, C. W. Rees and G. Tojo, *Tetrahedron Letters*, **28**, 3163 (1987); [h] D. L. Boger and R. S. Coleman, *J. Am. Chem. Soc.*, **109**, 2717 (1987); [i] D. L. Boger, R. S. Coleman and B. J. Invergo, *J. Org. Chem.*, **52**, 1521 (1987); [j] D. L. Boger and R. S. Coleman, *J. Org. Chem.*, **53**, 695 (1988); *idem.*, *ibid.*, **110**, 1321 (1988); [k] D. L. Boger and R. S. Coleman, *J. Am. Chem. Soc.*, **110**, 4796 (1988); [l] P. Carter, S. Fitzjohn, S. Halazy and P. Magnus, *J. Am. Chem. Soc.*, **109**, 1521 (1987); [m] M. A. Warpehoski and V. S. Bradford, *Tetrahedron Letters*, **27**, 2687 (1987); **29**, 131 (1988); [n] G. A. Kraus, S. Yue and J. Sy, *J. Org. Chem.*, **50**, 283 (1985); [o] R. J. Sundberg, G. S. Hamilton and J. P. Laurino, *J. Org. Chem.*, **53**, 976 (1988); [p] R. C. Kelly, I. Gebhard, N. Wicnienski, P. A. Aristoff, P. D. Johnson and D. G. Martin, *J. Am. Chem. Soc.*, **109**, 6837 (1987); [q] R. E. Bolton, C. J. Moody, M. Pass, C. W. Rees and G. Tojo, *J. Chem. Soc., Perkin Trans. I*, 2491 (1988).
- [4] D. H. Swenson, L. H. Li, Z. H. Hurley, J. S. Rokem, G. L. Petzold, B. D. Dayton, T. L. Wallace, A. H. Lin and W. C. Kreuger, *Cancer Res.*, **42**, 2821 (1982); L. H. Li, D. H. Swenson, S. L. F. Schpok, S. L. Kuentzel, B. D. Dayton and W. C. Kreuger, *Cancer Res.*, **42**, 999 (1982); V. L. Reynolds, I. J. Molineux, D. J. Kaplan, D. H. Swenson and L. H. Hurley, *Biochemistry*, **24**, 6228 (1985).
- [5] [a] L. H. Hurley, V. L. Reynolds, D. H. Swenson, G. L. Petzold and T. A. Scahill, *Science*, (Washington D.C.), **226**, 843 (1984); [b] D. R. Needham-vanDevanter, L. H. Hurley, V. L. Reynold, N. Y. Theriault, W. C. Kreuger and W. Wierenga, *Nucleic Acids Res.*, **12**, 6159 (1984).
- [6] For a recent discussion of sequence specific DNA binding agents: L. H. Hurley, *Ann. Rep. Med. Chem.*, **22**, 259 (1987).
- [7] J. P. McGovern, G. L. Clarke, E. A. Pratt and T. F. DeKoning, *J. Antibiot.*, **37**, 63 (1984).
- [8] [a] M. A. Warpehoski, *Tetrahedron Letters*, **27**, 4103 (1986); [b] M. A. Warpehoski, I. Gerhard, R. C. Kelly, W. L. Kreuger, L. H. Li, J. P. McGovern, M. D. Prairie, N. Wisneinski and W. Wierenga, *J. Med. Chem.*, **31**, 590 (1988); [c] L. H. Li, T. L. Wallace, T. F. DeKoning, M. A. Warpehoski, R. C. Kelly, M. D. Prairie and W. C. Kreuger, *Invest. New Drugs*, in press. [d] For a review of biological activity of analogs of CC-1065 see: W. Wierenga, B. K. Bhuyan, R. C. Kelly, W. L. Kreuger, L. H. Li, J. P. McGovern, D. H. Swenson and M. A. Warpehoski, *Adv. Enzyme Regul.*, **25**, 141 (1986).
- [9] G. A. Olah, M. Nojima and I. Kerekes, *Synthesis*, **607** (1973).
- [10] S. Rajesari, R. J. Jones and M. P. Cava, *Tetrahedron*, **28**, 5099 (1987).
- [11] S. M. Parmenter, A. G. Cook and W. B. Dixon, *J. Am. Chem. Soc.*, **80**, 4621 (1958).
- [12] Available from Aldrich Chemical Co., Inc.
- [13] Prepared by reacting an acetonitrile solution of **14** with half an equivalent of BSA at rt for 1 hour under nitrogen and evaporating the solvent *in vacuo*.
- [14] Spectroscopic data for this compound **20** was identical with that of the same reported earlier by Boger *et al.* [3j].
- [15] 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride.
- [16] Personal communication from Dr. Paul A. Aristoff, Associate Director, Cancer and Viral Diseases Research, The Upjohn Co., Kalamazoo.