Tetracyclic Benzodiazepines. 4. Synthesis of the Novel Benzo[c]pyrrolo[1,2,3-ef][1,5]benzodiazepine Ring System, and Derivatives with Potential Antipsychotic Activity

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The synthesis of the novel benzo[c]pyrrolo[1,2,3-ef][1,5]benzodiazepine ring system is described. This was achieved by cyclization of an appropriately substituted (7-aminoindolin-1-yl)benzamide or benzoic acid. The resulting tetracyclic lactams were reacted with *N*-methylpiperazine in the presence of titanium tetrachloride to provide derivatives which were tested for potential antipsychotic activity.

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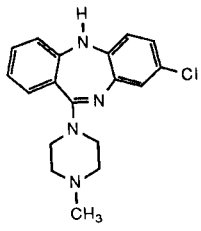
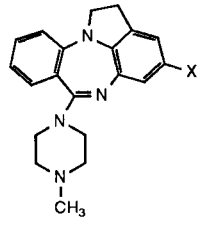
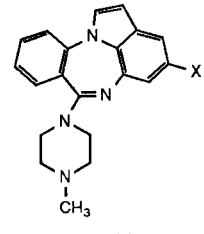
As part of our continuing program of synthesizing novel tetracyclic benzodiazepines of potential biological interest, we have recently turned our attention to the search for antipsychotic activity of the non-classical type exemplified by clozapine [1]. Clozapine (**I**) is unique within the class of antipsychotic agents because it does not cause the extrapyramidal side effects observed for the drugs currently used in the treatment of psychiatric disorders [2]. However, reports of agranulocytosis attributed to clozapine have limited its clinical utility [3]. With the hope of discovering a safer drug with a favorable clozapine-like therapeutic profile, we thought it would be of interest to synthesize the novel benzo[c]pyrrolo[1,2,3-ef][1,5]benzodiazepine ring system and several derivatives of type **II**.



I



IIa



IIb

The synthesis of the tetracyclic benzodiazepine ring system and derivatives bearing a nuclear chlorine atom is illustrated by Scheme 1. The nitrogen anion of 5-chloroindoline was generated by reaction with sodium hydride in dimethylsulfoxide. When heated at 75° with 2-fluorobenzamide, this anion displaced fluorine to form the (5-chloroindolin-1-yl)benzamide **1** in good yield. A nitro group was then introduced regioselectively into the 7-position of the indoline nucleus by using the silver nitrate/acetyl chloride reagent [4]. The nitro group of **2** was reduced by hydrogenation over 1% platinum-on-carbon catalyst at room temperature. Under these mild conditions, virtually no hydrogenolysis of the aromatic C-Cl bond was observed. The resulting product **3** now incorporated the appropriate functionalities for cyclization into the novel 1,2-dihydrobenzo[c]pyrrolo[1,2,3-ef][1,5]benzodiazepine ring system. Upon heating at 150° an intimate mixture of **3** with silica gel as a catalytic surface, ammonia was extruded to form the 7-membered central ring in 61% yield. The lactam product **4** could be dehydrogenated by heating with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in xylene to provide the precursor **5** for a subgroup of 1,2-dehydro tetracyclic derivatives with a fully unsaturated nucleus (**9** and **10** of Table II). In the final step of the synthesis, the pendant *N*-methylpiperazine moiety found in clozapine was introduced by the procedure of Fryer *et al.* [5]. This involved heating lactam **4** or **5** in toluene with the amine and titanium tetrachloride as catalyst to promote the condensation. In order to broaden structure-activity relationships, several other heterocyclic amines were similarly introduced at the 7-position of the central ring (see **7**, **8** and **10** of Table II).

From other work in this area [6], we found that a nuclear methyl substituent could confer enhanced antipsychotic properties in a related series of molecules. Accordingly, it was of interest to prepare several analogs in the present series with a CH_3 instead of Cl at nuclear position 4. The synthesis of this group of compounds was somewhat different and is shown in Scheme 2. Condensation of 5-methylindoline with 2-fluorobenzonitrile, followed by nitration of the product **11**, was carried out as described previously in the chloro series. In the next step, the cyano group of **12** was hydrolyzed to a carboxylic acid by heating with potassium hydroxide in ethylene glycol. The resulting nitro-acid **13** was reduced catalytically in the presence of a few drops of concentrated hydrochloric acid. Under these conditions, as soon as the amine formed it underwent cyclodehydration with the adjacent carboxylic acid moiety to form lactam **14**. Dehydrogenation of the latter with DDQ furnished the unsaturated lactam **15**. Both lactams were then reacted with *N*-methylpiperazine and titanium tetrachloride to provide the target molecules **16** and **17** with a nuclear methyl substituent.

Scheme 1

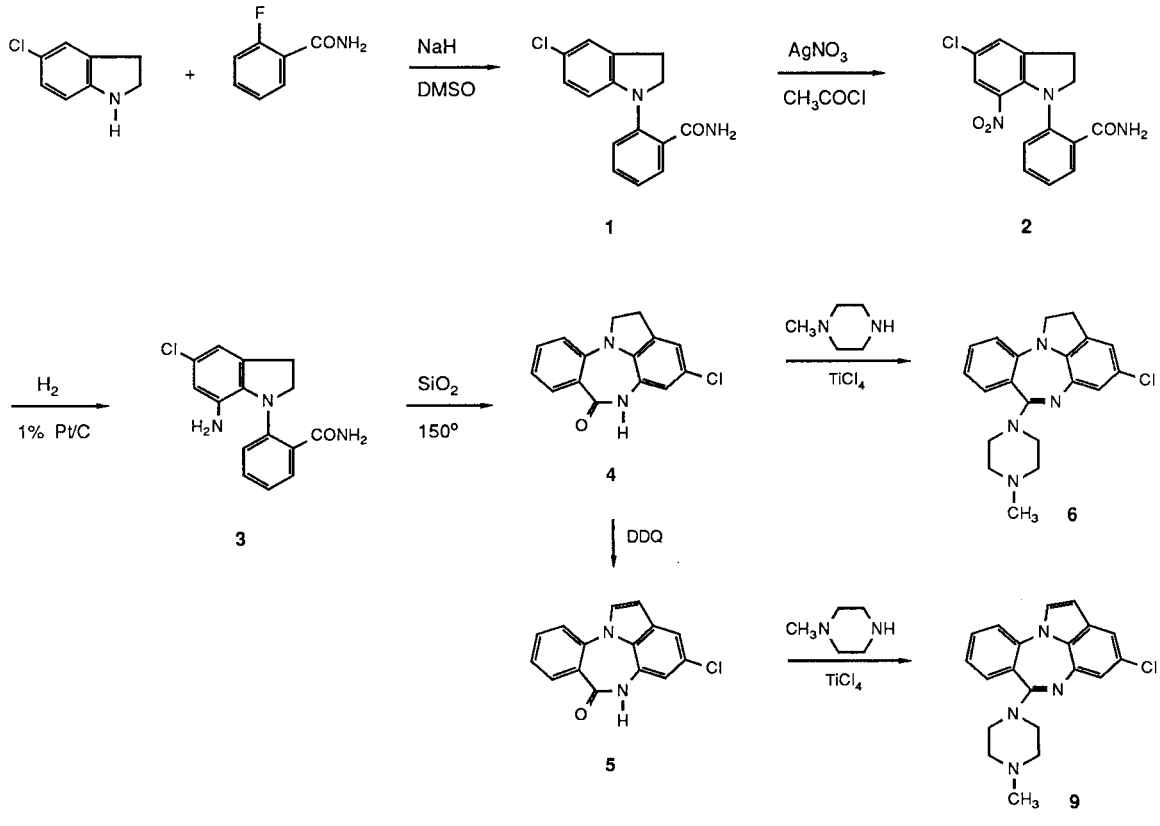
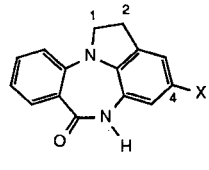


Table I

Lactam Intermediates: 4-Substituted-1,2-dihydro(and 1,2-dehydro)benzo[*c*]pyrrolo[1,2,3-*ef*][1,5]benzodiazepin-7-ones



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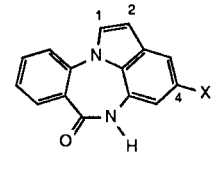

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Compound	X	Mp (°C)	Yield % [a]	Recrystallization Solvent	Molecular Formula	Analyses, % Calcd./Found C	H	N
4	Cl	252-255	61	chloroform	$C_{15}H_{11}ClN_2O$	66.55 66.85	4.10 4.14	10.35 10.38
5	Cl	278-280	54	ethanol	$C_{15}H_9ClN_2O$	67.05 66.74	3.38 3.45	10.42 10.39
14	CH_3	222-224	66	chloroform	$C_{16}H_{14}N_2O$	76.76 76.41	5.64 5.63	11.12 11.21
15	CH_3	229-230	75	[b]	$C_{16}H_{12}N_2O$	77.40 77.15	4.87 5.01	11.28 11.18

[a] These yields represent analytically pure products. No attempt was made to optimize yields. [b] After chromatography, this compound was obtained in a pure crystalline state by evaporation of the eluent.

Scheme 2

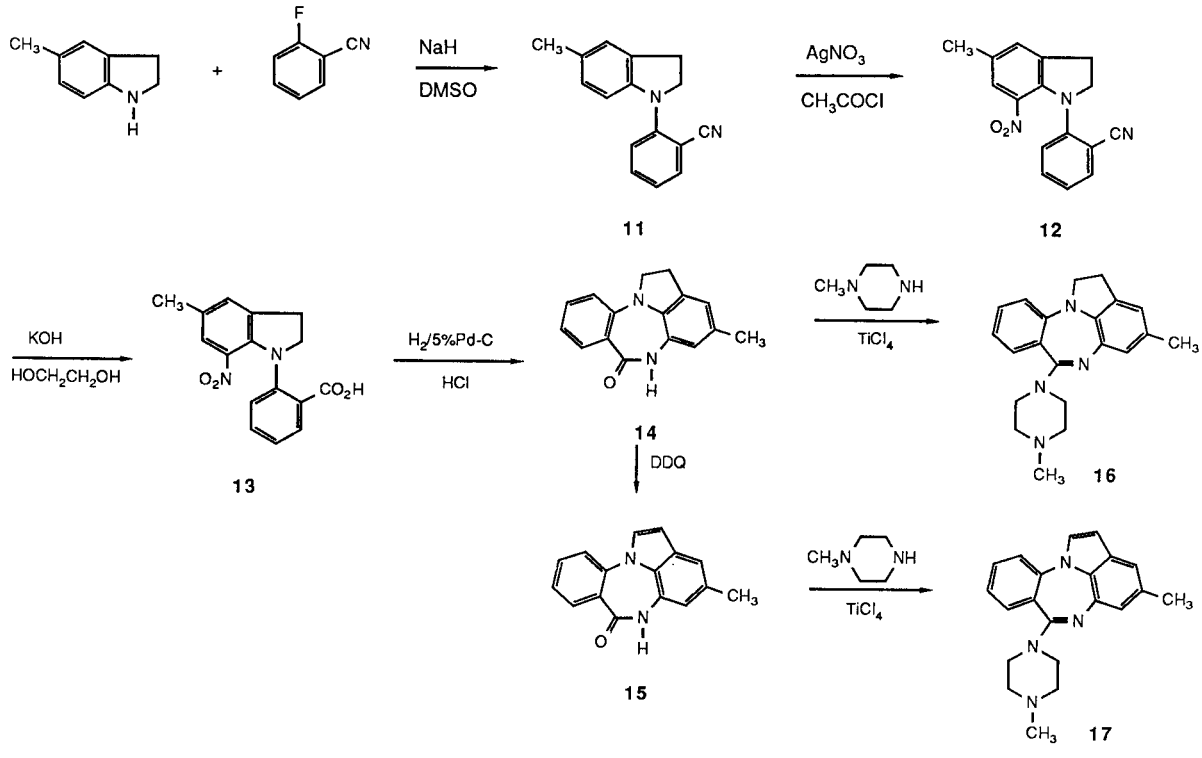
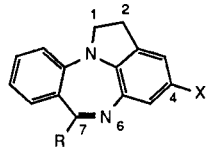
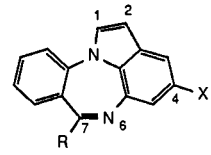


Table II

7-Substituted-1,2-dihydro(and 1,2-dehydro)benzo[*c*]pyrrolo[1,2,3-*ef*][1,5]benzodiazepines



6-8,16



9,10,17

Compound	X	R	Mp (°C)	Yield [a] %	Recrystallization Solvent	Molecular Formula	Analyses, % Calcd./Found C	H	N
6	Cl	-N N-CH_3	199-201	45	ethanol	$C_{20}H_{21}ClN_4$	68.08 68.37	6.00 6.08	15.88 15.97
7	Cl	-N N-C_6H_5	138-141	47	ethanol	$C_{25}H_{23}ClN_4$	72.37 72.37	5.59 5.65	13.50 13.40
8	Cl	-N CH_3	238-239	36	dichloromethane	$C_{21}H_{22}ClN_3$	71.68 71.82	6.30 6.29	11.94 12.17
9	Cl	-N N-CH_3	184-186	78	dichloromethane hexane	$C_{20}H_{19}ClN_4$	68.47 68.19	5.46 5.48	15.97 15.83
10	Cl	-N CH_3	162-163	75	dichloromethane hexane	$C_{21}H_{20}ClN_3$	72.09 72.14	5.76 5.83	12.01 12.02
16	CH_3	-N N-CH_3	173-174	70	2-propanol	$C_{21}H_{24}N_4$	75.87 75.52	7.28 7.32	16.85 16.69
17	CH_3	-N N-CH_3	167-168	61	2-propanol	$C_{21}H_{22}N_4$	76.33 76.28	6.71 6.84	16.96 16.84

[a] These yields represent analytically pure products. No attempt was made to optimize these yields.

The tetracycles of Table II, each bearing an *N*-methylpiperazine or related substituent at the central ring, were tested for potential antipsychotic activity in the Climbing Mouse Assay [7]. This animal model will detect classical antipsychotics such as haloperidol, as well as those with an atypical profile such as clozapine [8]. All of the compounds of Table II were found to be less active than the corresponding members of an isomeric series of benzo[*b*]pyrrolobenzodiazepines [6].

EXPERIMENTAL

Melting points were determined using a Thomas-Hoover Uni-melt apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 457 grating spectrometer. Nuclear ^1H magnetic resonance spectra were taken on a Varian XL-200 Spectrometer. Chemical shift values are reported in δ units (parts per million) relative to tetramethylsilane as an internal standard. Mass spectra were obtained from a Finnigan Model 4000 spectrometer interfaced to a Finnigan 9610 gas chromatograph and equipped with an INCOS data system. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Illinois. Chromatography was carried out with E. Merck products using silica gel 60 (catalog No. 7734) for open column chromatography and silica gel catalog No. 9385 for flash chromatography.

The final yields reported here and in the Tables represent analytically pure products. No effort was made to optimize the yields.

2-(5-Chloro-2,3-dihydro-1*H*-indol-1-yl)benzamide (**1**).

To a stirred solution, under nitrogen, of 15.3 g (0.10 mole) of 5-chloroindoline in 50 ml of dimethylsulfoxide (DMSO) was added 5.28 g of sodium hydride (50% in oil, 2.64 g pure, 0.11 mole). The slurry was stirred for 1 hour and then a solution of 15.2 g (0.11 mole) of 2-fluorobenzamide in 20 ml of DMSO was added dropwise over a 30 minute period. When the addition was completed, the reaction mixture was stirred at room temperature for an additional two hours, and then heated at 75-78° overnight (16 hours). It was then cooled and partitioned between 300 ml of dichloromethane and 250 ml of water. The aqueous phase was separated and extracted further with dichloromethane (2 × 150 ml). The organic extracts were combined, washed with water (2 × 100 ml), with 2*N* hydrochloric acid (2 × 100 ml), twice with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then concentrated to a volume of about 50 ml. Ether (50 ml) was added and the product was allowed to crystallize overnight. This provided 14.2 g (52%) with mp 137-138°. Recrystallization from dichloromethane/ether furnished 11.8 g of pure **1**, mp unchanged, in 43% overall yield; ir (potassium bromide): 3350, 3140 (NH_2), 1660 (C=O), 1590 (aromatic C=C), 1480, 1370, 1250, 820 cm^{-1}; nmr (deuteriochloroform): δ 3.17 (t, 2H, CH_2), 3.84 (t, 2H, N-CH_2), 6.40-8.26 (m, 7H, Ar-H), 6.47, 8.36 (2s, 1H each, $CONH_2$, partially exchangeable with deuterium oxide); ms: ci/methane (% relative abundance) 273 (MH^+, 100), 256 (84), 239 (24), 222 (19).

Anal. Calcd. for $C_{15}H_{13}ClN_2O$: C, 66.06; H, 5.01; N, 10.29. Found: C, 65.69; H, 4.92; N, 10.18.

2-(5-Chloro-2,3-dihydro-7-nitro-1*H*-indol-1-yl)benzamide (**2**).

A solution of 11.9 g (43.6 mmoles) of benzamide **1** and 8.16 g (48 mmoles) of silver nitrate in 50 ml of chloroform and 100 ml of acetonitrile was stirred and cooled under nitrogen to 15°. To this was added dropwise a solution of 3.80 g (48 mmoles) of acetyl chloride in 10 ml of acetonitrile over a 20 minute period. After stirring at room temperature for 3 hours, the reaction mixture was diluted with 250 ml of dichloromethane and then it was filtered. The yellow solid (silver chloride) was washed several times with a large volume of dichloromethane (total of 1.2 ℓ). The reaction filtrate and the washes were combined and extracted with aqueous sodium chloride solution containing 5 g of sodium bicarbonate (2 × 125 ml). The organic phase was dried over anhydrous sodium sulfate and concentrated to 14.9 g of solid. Recrystallization from chloroform-ether (1:1) afforded 12.6 g of red-orange crystals (77%) of nitrobenzamide, mp 225-226°; ir (potassium bromide): 3445, 3160 (NH_2), 1665 (C=O), 1590 (aromatic C=C), 1520, 1460, 1360, 1320, 755 cm^{-1}; nmr (DMSO-d_6): δ 3.18-3.36 (m, 2H, CH_2), 3.92, 4.24 (2q, 2H, N-CH_2), 7.13-7.70 (m, 8H, 6 Ar-H, $CONH_2$, partially exchangeable with deuterium oxide); ms: m/e (% relative abundance) 317 (M^+, 10), 270 (11), 253 (79), 239 (98), 219 (10), 191 (27), 135 (11), 95 (21), 83 (100), 47 (37).

Anal. Calcd. for $C_{15}H_{12}ClN_3O_3 \cdot 0.5\ CHCl_3$: C, 49.33; H, 3.34; N, 11.13. Found: C, 49.67; H, 3.39; N, 11.24.

2-(7-Amino-5-chloro-2,3-dihydro-1*H*-indol-1-yl)benzamide (**3**).

A Parr hydrogenation bottle was charged with 10.0 g (26.5 mmoles) of nitrobenzamide **2**, 2.00 g of 1% platinum-on-carbon catalyst, and 100 ml each of ethanol and dimethylformamide. The mixture was shaken under an initial hydrogen pressure of 59 psi for 4.5 hours. The reaction was then filtered to remove the catalyst and the filtrate was concentrated at 55° *in vacuo* to a pink solid. This was purified by recrystallization twice from chloroform to afford 4.30 g (54%) of pure white **3** with mp 199-201° dec; ir (potassium bromide): 3465, 3400, 3360, 3240 ($ArNH_2$, $CONH_2$, HOH), 1650 (C=O), 1600 (aromatic C=C), 1480, 1280, 760 cm^{-1}; nmr (deuteriochloroform + DMSO-d_6): δ 2.80-4.28 (m, 4H, CH_2, N-CH_2), 3.90 (s, 2H, Ar-NH_2, exchangeable with deuterium oxide), 6.57-8.02 (m, 6H, Ar-H), 6.84, 8.36 (2s, 1H each, $CONH_2$, partially exchangeable with deuterium oxide); ms: m/e (% relative abundance) 289 ($M^+ + 2$, 22), 288 ($M^+ + 1$, 6), 287 (M^+, 100), 270 (18), 255 (3), 242 (4), 234 (6), 206 (5).

Anal. Calcd. for $C_{15}H_{14}ClN_3O \cdot 0.5\ H_2O$: C, 60.71; H, 5.06; N, 14.16. Found: C, 60.51; H, 4.68; N, 14.32.

4-Chloro-1,2-dihydrobenzo[*c*]pyrrolo[1,2,3-*ef*][1,5]benzodiazepin-7-one (**4**).

A large single-neck round bottom flask was charged with 28.7 g (96.7 mmoles) of 2-(7-amino-5-chloro-2,3-dihydro-1*H*-indol-1-yl)benzamide **3** and a sufficient volume of 10% methanol in dichloromethane to effect solution with warming. Silica gel (510 g) was added to absorb the starting material and the solvent was removed on a rotovac at 50° over the course of 1 hour. The flask was then immersed in an oil bath kept at 145-155° and the silica gel mixture was stirred mechanically at that temperature for 1.5 hours. The flask was left open so that the vapor liberated could freely escape. Heating was stopped when the mixture began to turn brown. The silica gel mixture was then cooled and placed on top of a flash chromatography column containing 1 kg of silica gel slurry-packed with dichloromethane (DCM). The column was eluted with 16 ℓ of DCM, followed by 10 ℓ of 2% methanol in DCM. The fractions containing the purified product were combined and concentrated to an orange-red solid. This was recrystallized from chloroform to provide 16.0 g of pure **4** in 61% overall yield, mp 252-255°; ir (potassium bromide): 3200 (NH), 1650 (C=O), 1615 (aromatic C=C), 1485, 1380, 1160, 740 cm^{-1}; nmr (DMSO-d_6): δ 3.02 (t, 2H, CH_2), 3.78 (t, 2H, N-CH_2), 6.72-7.92 (m, 6H, Ar-H), 9.80 (s, 1H, N-H, exchangeable with deuterium oxide); ms: m/e (% relative abundance) 272 ($M^+ + 2$, 27), 271 ($M^+ + 1$, 15), 270 (M^+, 100), 234 (20), 206 (10).

4-Chlorobenzo[*c*]pyrrolo[1,2,3-*ef*][1,5]benzodiazepin-7-one (**5**).

To a stirred solution of 7.00 g (25.9 mmoles) of 4-chloro-1,2-dihydro lactam **4** in 800 ml of xylene at 100-105° was added 7.00 g (31 mmoles) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in one portion. The mixture was refluxed for 2.5 hours, and then it was filtered rapidly through a course-grade sintered glass funnel. After cooling the filtrate to 5°, the crystals were collected and washed with 10 ml of ethanol to provide 5.8 g (83%) of product. Recrystallization from 800 ml of hot ethanol afforded 3.80 g of yellow needles, mp 278-280° in 54% overall yield; ir (potassium bromide): 3200 (NH), 1660 (C=O), 1620, 1590, 1470, 1250, 850, 825, 742, 720 cm^{-1}; nmr (DMSO-d_6): δ 6.68 (d, 1H, C_2-H), 6.78-8.16 (m, 7H, 6Ar-H + C_1-H), 11.4 (s, 1H, N-H); ms; m/e (% relative abundance) 270 ($M^+ + 2$, 31), 269 ($M^+ + 1$, 19), 268 (M^+, 100), 239 (11), 233 (14), 205 (15), 177 (4), 102 (6), 75 (4).

4-Chloro-1,2-dihydro-7-(4-methyl-1-piperazinyl)benzo[*c*]pyrrolo[1,2,3-*ef*][1,5]benzodiazepine (**6**).

A stirred mixture of 3.50 g (12.9 mmoles) of 4-chloro lactam **4** and 12.9 g (129 mmoles) of *N*-methylpiperazine in 250 ml of toluene was heated under nitrogen to 100°. Then 3.5 ml (32.2 mmoles) of titanium tetrachloride was added and the mixture was refluxed for 2 hours. The mixture was then cooled and partitioned between 500 ml of ether and 600 ml of water, with stirring. The insoluble material was removed by filtration. The organic phase was separated, washed twice with saturated aqueous sodium chloride solution, was dried over anhydrous sodium sulfate and concentrated to a yellow solid (4.3 g). This material was purified by flash chromatography over 200 g of silica gel packed and eluted (1.5 ℓ) with 4% methanol in dichloromethane. The appropriate fractions were combined and concentrated to afford 2.6 g of virtually pure product. Recrystallization from ethanol provided 2.05 g of yellow crystals of pure **6** in 45% overall yield with mp 199-201°; ir (chloroform): 1595, 1580 (aromatic C=C; C=N), 1450, 1250 cm^{-1}; nmr (deuteriochloroform): δ 2.38 (s, 3H, N-CH_3), 2.52 (tight m, 4H, piperazine CH_2), 3.00 (t, 2H, CH_2), 3.48 (tight m, 4H, piperazine CH_2), 3.92 (t, 2H, N-CH_2), 6.78-7.36 (m, 6H, Ar-H); ms: m/e (% relative abundance) 352 (M^+, 17), 282 (44), 269 (100), 254 (22), 218 (31), 70 (14).

Prepared in a similar manner were the other 1,2-dihydro-4-chloro compounds described in Table II:

4-Chloro-1,2-dihydro-7-(4-phenyl-1-piperazinyl)benzo[*c*]pyrrolo[1,2,3-*ef*][1,5]benzodiazepine (**7**).

This compound was prepared from lactam **4** using *N*-phenylpiperazine. The crude product did not require chromatographic purification. Simple recrystallization of the extraction product provided analytically pure **7**.

4-Chloro-1,2-dihydro-7-(4-methyl-1-piperidinyl)benzo[*c*]pyrrolo[1,2,3-*ef*][1,5]benzodiazepine (**8**).

This analog was prepared from **4** using 4-methylpiperidine as base. The crude extraction product was not chromatographed but was recrystallized to afford pure **8**.

Also prepared by the same procedure described for **6** were the following 1,2-dehydro-4-chloro derivatives of Table II:

4-Chloro-7-(4-methyl-1-piperazinyl)benzo[*c*]pyrrolo[1,2,3-*ef*][1,5]benzodiazepine (**9**).

This compound was prepared from the unsaturated 4-chloro lactam **5**. The crude product did not require a flash chromatography prior to recrystallization.

4-Chloro-7-(4-methyl-1-piperidinyl)benzo[*c*]pyrrolo[1,2,3-*ef*][1,5]benzodiazepine (**10**).

This compound was prepared and purified in the same way as **6** except that 4-methylpiperidine was used in the condensation with unsaturated lactam **5**.

2-(2,3-Dihydro-5-methyl-1*H*-indol-1-yl)benzonitrile (**11**).

A slurry of 31.0 g (0.233 mole) of 5-methylindoline and 11.3 g of sodium hydride (60% in oil, 6.78 g pure, 0.283 mole) in 120 ml of dimethylsulfoxide was stirred under nitrogen for 1 hour. To this was added dropwise a solution of 31.0 g (0.256 mole) of 2-fluorobenzonitrile in 25 ml of dimethylsulfoxide while maintaining the temperature below 20°. When the addition was completed, the reaction was stirred for 2 hours at room temperature, and then it was poured into a well stirred mixture of 700 ml of dichloromethane and 700 ml of ice water. The phases were separated and the aqueous layer was extracted further with dichloromethane (2 × 600 ml). The organic phases were combined, washed with 2*N* hydrochloric acid (2 × 500 ml), with 500 ml of water and with saturated aqueous sodium chloride solution (2 × 400 ml). The organic phase was then dried over anhydrous sodium sulfate and concentrated to 50 g of oil. This was dissolved in 300 ml of ethanol and 100 ml of heptane, and chilled in the refrigerator overnight to afford 7.0 g of pure needles of the product **11**. The mother liquor was concentrated and purified by flash chromatography using 400 g of silica gel and eluting with 3 ℓ of 25% dichloromethane in hexane, 2 ℓ of 50% dichloromethane in hexane and finally with 2 ℓ of dichloromethane. The fractions containing the product were combined and concentrated to an oil weighing 33 g. This was purified further with a 2-chambered HPLC-Prep 500 using 10% dichloromethane in hexane as eluent. The resulting oil crystallized from ethanol to provide 7.1 g. The first and second crops combined yielded 14.1 g (26% overall) of pale yellow crystals of pure **11** with mp 59-60°; ir (chloroform): 2240 (C≡N), 1600 (aromatic C=C), 1490 cm^{-1}; nmr (deuteriochloroform): δ 2.32 (s, 3H, CH_3), 3.16 (t, 2H, CH_2), 4.15 (t, 2H, NCH_2), 6.78-7.64 (m, 7H, Ar-H); ms: m/e (% relative abundance) 234 (M^+, 100), 233 (97), 219 (19), 116 (11), 102 (5), 77 (5), 72 (8).

Anal. Calcd. for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02; N, 11.96. Found: C, 82.47; H, 6.08; N, 12.10.

2-(2,3-Dihydro-5-methyl-7-nitro-1*H*-indol-1-yl)benzonitrile (**12**).

By following the same nitration procedure described for **2** but using 13.9 g (59 mmoles) of 2-(2,3-dihydro-5-methyl-1*H*-indol-1-yl)benzonitrile **11**, 11.0 g (64.7 mmoles) of silver nitrate and 5.60 g (71 mmoles) of acetyl chloride, there was obtained after recrystallization from ethanol 12.3 g of pure **12**, mp 138-139°, in 75% yield; ir (chloroform): 2230 (C≡N), 1595, 1580, 1515, 1485, 1360, 1330 cm^{-1}; nmr (DMSO-d_6): δ 2.34 (s, 3H, CH_3), 3.30 (m, 2H, CH_2), 3.92 , 4.44 (2 broad s, 1H each, N-CH_2), 7.08-8.92 (m, 6H, Ar-H); ms: m/e (% relative abundance) 279 (M^+, 100), 233 (59), 218 (41), 205 (9), 190 (5), 116 (7), 102 (9), 77 (9), 63 (5), 51 (9).

Anal. Calcd. for $C_{16}H_{13}N_2O_3$: C, 68.81; H, 4.69; N, 15.04. Found: C, 68.89; H, 4.79; N, 15.23.

2-(2,3-Dihydro-5-methyl-7-nitro-1*H*-indol-1-yl)benzoic Acid (**13**).

A stirred mixture of 26.0 g (93 mmoles) of benzonitrile **12** and 30 g of potassium hydroxide in 35 ml of water and 250 ml of ethylene glycol was heated at 175° for 3 hours. The reaction was then cooled to room temperature and decanted into a well stirred mixture of 1 ℓ of dichloromethane and 500 ml of ice/water. The aqueous phase was separated and extracted twice with 250 ml portions of dichloromethane. The aqueous phase was then cooled and acidified with hydrochloric acid. The product acid was extracted into dichloromethane (3 × 500 ml) and the organic solution was washed with saturated aqueous sodium chloride solution (2 × 300 ml), was dried over anhydrous sodium sulfate and concentrated to an oil weighing 9.0 g (33% yield). This acid **13** was used as is to prepare the 4-methyl lactam **14**.

From the initial dichloromethane phase was isolated 14 g (50% yield) of the other reaction product, resulting from incomplete hydrolysis, 2-(2,3-dihydro-5-methyl-7-nitro-1*H*-indol-1-yl)benzamide, mp 173-175°.

1,2-Dihydro-4-methylbenzo[*c*]pyrrolo[1,2,3-*ef*][1,5]benzodiazepin-7-one (**14**).

A Parr bottle was charged with 9.00 g (0.030 mole) of 2-(2,3-dihydro-5-methyl-7-nitro-1*H*-indol-1-yl)benzoic acid **13**, 200 ml of absolute ethanol, 1.5 g of 5% palladium-on-charcoal catalyst and several drops of concentrated hydrochloric acid. The mixture was shaken under 58 psi of hydrogen for 30 hours. The solvent was then removed on the rotary evaporator and the residue was loaded onto a flash chromatography column containing 800 g of silica gel packed with dichloromethane (DCM). The column was eluted with 4 ℓ of DCM followed by 4 ℓ of 2% methanol in DCM. The fractions containing the pure product were combined and concentrated to a red crystalline solid. Recrystallization from chloroform furnished 5.00 g of pure lactam, mp 222-224°, in 66% overall yield; ir (chloroform): 3390 (NH), 1645 (C=O), 1620, 1490 cm^{-1}; nmr (deuteriochloroform): δ 2.20 (s, 3H, CH_3), 3.04 (t, 2H, CH_2), 3.76 (t, 2H, NCH_2), 6.56-8.06 (m, 6H, Ar-H); ms: m/e (% relative abundance) 250 (M^+, 100), 249 (33), 234 (8), 221 (7), 206 (11), 125 (8), 109 (8), 103 (17), 97 (10), 69 (15), 57 (11).

4-Methylbenzo[*c*]pyrrolo[1,2,3-*ef*][1,5]benzodiazepin-7-one (**15**).

This compound was prepared by the same procedure already described for the other unsaturated lactam **5** of Table II except that **14** was the

starting material and the crude product was purified by flash chromatography over silica gel using dichloromethane as eluent.

1,2-Dihydro-4-methyl-7-(4-methyl-1-piperazinyl)benzo[*c*]pyrrolo[1,2,3-*ef*][1,5]benzodiazepine (**16**).

This compound was prepared in the same fashion as **6** except that the 4-methyl lactam **14** was used as substrate. Its physical properties are listed in Table II.

4-Methyl-7-(4-methyl-1-piperazinyl)benzo[*c*]pyrrolo[1,2,3-*ef*][1,5]benzodiazepine (**17**).

A stirred mixture of 3.20 g (12.9 mmoles) of 1,2-dehydro-4-methyl lactam **15** and 12.9 g (129 mmoles) of *N*-methylpiperazine in 300 ml of toluene was heated under nitrogen until a solution resulted (at 100-110°). Then 4.5 ml (41 mmoles) of titanium tetrachloride was added, and the mixture was refluxed for 1 hour. The reaction was then cooled to room temperature and 500 ml of toluene and 1000 ml of ice-water were added. After stirring for 15 minutes, the insoluble material was removed by filtration. The organic phase was separated, washed three times with saturated aqueous sodium chloride solution, was dried over anhydrous sodium sulfate and concentrated to a yellow solid. This material was purified by flash chromatography over 200 g of silica gel packed and eluted with 2.5% methanol in dichloromethane. The fractions containing product were combined and concentrated to 2.8 g of crystals. Recrystallization from 2-propanol furnished 2.6 g of pure **17** as yellow crystals in 61% overall yield with mp 167-168°; ir (chloroform): 1605 (aromatic C=C), 1580, 1260, 1140 cm^{-1}; nmr (deuteriochloroform): δ 2.30 (s, 3H, Ar-CH_3), 2.36 (s, 3H, N-CH_3), 2.50 (tight m, 4H, piperazine CH_2), 3.44 (tight m, 4H, piperazine CH_2), 6.48 (d, 1H, C_2-H), 6.75-7.46 (m, 7H, 6Ar-H + C_1-H); ms: m/e (% relative abundance) 330 (M^+, 16), 272 (7), 260 (36), 247 (100), 231 (48), 216 (18), 204 (3), 143 (7), 99 (4), 70 (10).

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REFERENCES AND NOTES

[1] For the previous article in this series, see: E. J. Glamkowski and Y. Chiang, *J. Heterocyclic Chem.*, **24**, 733 (1987).

[2] B. Shopsin, H. Klein, M. Aaronsom, and M. Collora, *Arch. Gen. Psychiatry*, **36**, 657 (1979) and references therein.

[3] J. Indänpään-Heikkilä, E. Alhava, M. Olkinuora, and I. Palva, *Lancet*, **2**, 611 (1975).

[4] N. R. Raulins, W. G. Kruggel, D. D. Titus, and D. C. Van Landuyt, *J. Heterocyclic Chem.*, **5**, 1 (1968).

[5] R. I. Fryer, J. V. Earley, G. F. Field, W. Zally, and L. H. Sternbach, *J. Org. Chem.*, **34**, 1143 (1969).

[6] E. J. Glamkowski, Y. Chiang, M. Cornfeldt, R. W. Dunn, H. M. Geyer III, and F. P. Huger, 193rd ACS National Meeting, Denver, Colorado, April 5-10 (1987): Abstracts MEDI 75. Full manuscript is in preparation.

[7] J. T. Strupczewski, R. C. Allen, B. A. Gardner, B. L. Schmid, U. Stache, E. J. Glamkowski, M. C. Jones, D. B. Ellis, F. P. Huger, and R. W. Dunn, *J. Med. Chem.*, **28**, 761 (1985) except that dosing in the present work was orally at 40 mg/kg with a pretreat time of one hour.

[8] B. Costall, R. J. Naylor, and V. Nohria, *Eur. J. Pharmacol.*, **50**, 39 (1978).