

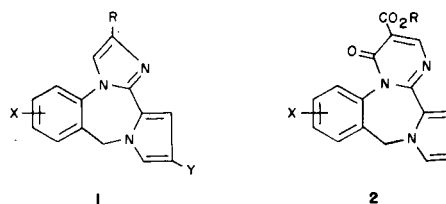
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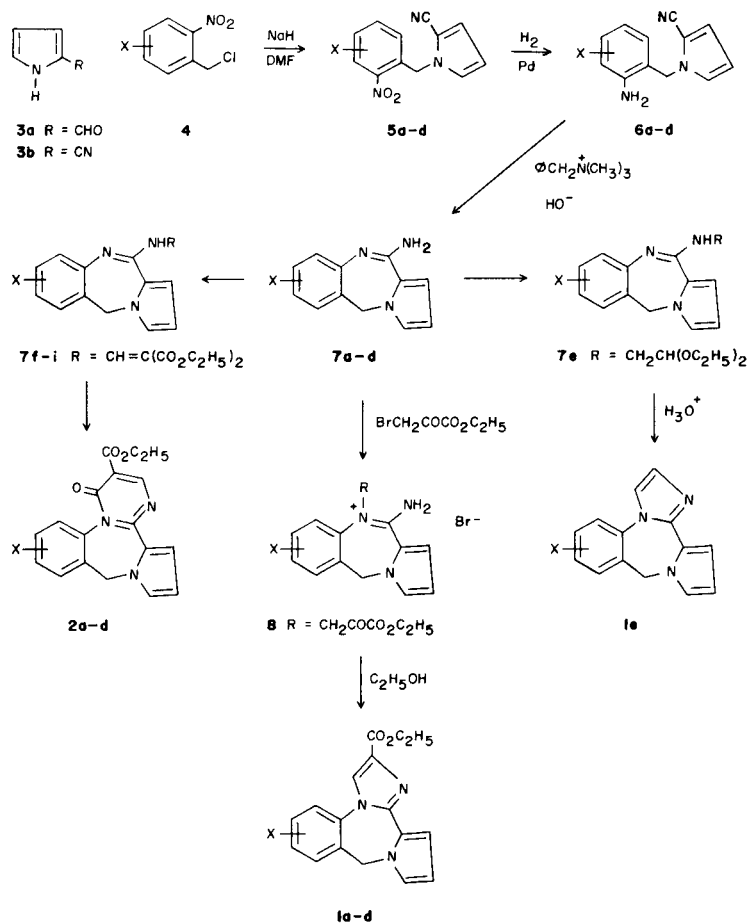
Several 11-amino-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepines have been used as starting material to prepare a number of derivatives of 9*H*-imidazo[1,2-*a*]pyrrolo[2,1-*c*][1,4]benzodiazepines and 10*H*-pyrimido[1,2-*a*]pyrrolo[2,1-*c*][1,4]benzodiazepines. The imidazole nucleus was built by reaction of amidines with ethyl bromopyruvate or aminoacetaldehyde dimethylacetal. Several derivatives of imidazo[1,2-*a*]pyrrolo[2,1-*c*][1,4]benzodiazepine have been prepared by formylation of the pyrrole ring followed by formation of thioamides. Condensation of 11-amino-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepines with diethyl ethoxymethylenemalonate afforded intermediate diesters which were transformed into the corresponding 10*H*-pyrimido[1,2-*a*]pyrrolo[2,1-*c*][1,4]benzodiazepines.

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The reported antigastric activity [2] and antiallergy properties [3-6] of imidazoles and pyrimidones stimulated the search in this laboratory for other novel heterocycles incorporating these ring systems. This prompted the synthesis of imidazo[1,2-*a*]pyrrolo[2,1-*c*][1,4]benzodiazepines **1** and pyrimido[1,2-*a*]pyrrolo[2,1-*c*][1,4]benzodiazepines **2**.



Scheme 1



Wright *et al.* [7] have reported a synthesis of 1-(2-nitrobenzyl)-2-pyrrolicarbonitriles **5a-c** in three steps *via* formation of an intermediate oxime starting from 2-pyrrolicarboxaldehyde **3a**. We have improved their procedure using 2-pyrrolicarbonitrile **3b** [8] and arylsubstituted 2-nitrobenzyl chlorides **4** as starting materials. The 1-(2-(aminobenzyl)-2-pyrrolicarbonitriles **6a-d** were prepared by catalytic reduction of the corresponding nitro derivatives **5a-d** using palladium on charcoal in methanol (Scheme 1, Table 1). The preparation of amidines **7a-d** was done in good yield under mild conditions by cyclization of aminobenzyl derivatives **6a-d** using benzyltrimethylammonium hydroxide in toluene (Scheme 1, Table II). We have developed two procedures to prepare tetracyclic imidazoles **1**. The first method involves the formation of benzodiazepinium bromides **8** by reaction of amidines **7a-d** with ethyl bromopyruvate followed by cyclodehydration in boiling ethanol to afford imidazoles **1a-d** in good yield. The second method involves the preparation of amidinoketal **7e** from amidine **7a** with aminoacetaldehyde dimethylacetal and ammonium chloride in toluene under reflux conditions. A final treatment of amidine **7e** with dilute mineral acid at reflux afforded imidazole **1e** in excellent yield (Scheme 1, Table III).

Imidazoles **1a** and **1e** were readily formylated under standard Vilsmeier conditions to afford 9*H*-imidazo[1,2-*a*]pyrrolo[2,1-*c*][1,4]benzodiazepine-12-carboxaldehydes **1f-g** (Scheme 2, Table III).

The position of the aldehyde group in **1f** has been ascertained by nmr analysis of the H₁₁ and H₁₃ protons of the pyrrole ring (Figure 1) where the chemical shifts of H₁₁ and H₁₃ are δ (7.30 and 7.92 ppm) and coupling constant

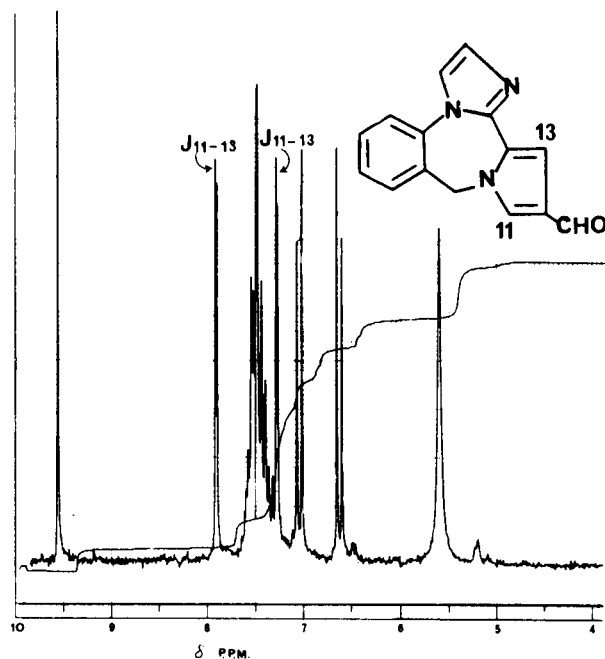
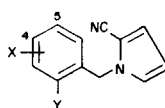


Figure 1. ¹H-nmr spectrum of 9*H*-imidazo[1,2-*a*]pyrrolo[2,1-*c*][1,4]benzodiazepine-12-carboxaldehyde.

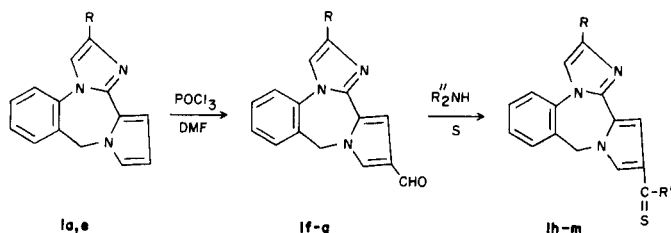
Table 1

Aryl Substituted-2-pyrrolicarbonitriles



Compound No.	X	Y	Mp °C	Recrystallization Solvent	Yield %	Formula	Analysis %		
							Calcd./	Found	N
5a	H	NO ₂	92-94	Ether-hexane	91	C ₁₂ H ₉ N ₃ O ₂ 227.22	lit [7] mp	95-96°	
5b	4-Cl	NO ₂	86-87	Ether-hexane	33	C ₁₂ H ₈ ClN ₃ O ₂ 261.67	lit [7] mp	93-95°	
5c	5-Cl	NO ₂	133-134	Ether-hexane	92	C ₁₂ H ₈ ClN ₃ O ₂ 261.67	lit [7] mp	134-136°	
5d	5-CH ₃	NO ₂	97-98	Ether-hexane	70	C ₁₃ H ₁₁ N ₃ O ₂ 241.24	64.72 64.77	4.60 4.60	17.42 17.46
6a	H	NH ₂	64-64.5	Ether-hexane	77	C ₁₂ H ₁₁ N ₃ 197.23	lit [7] mp	60-61°	
6b	4-Cl	NH ₂	79-81	Ether-hexane	41	C ₁₂ H ₁₀ ClN ₃ 231.68	lit [7] mp	77-79°	
6c	5-Cl	NH ₂	127-128	Ether-hexane	25	C ₁₂ H ₁₀ ClN ₃ 231.68	lit [7] mp	130-132°	
6d	5-CH ₃	NH ₂	111-112	Cyclohexane	93	C ₁₃ H ₁₃ N ₃ 211.25	73.91 73.73	6.20 6.21	19.89 19.88

Scheme 2



value $J_{11-13} = 1.4$ Hz compares very well with similarly substituted pyrrole derivatives such as 4-formyl-2-pyrrole-carbonitrile δ (7.29 and 7.88 ppm) and $J = 1.5$ Hz [9].

Several thioamide derivatives **1h-m** have been prepared by subjecting aldehydes **1f-g** under Willgerodt-Kindler conditions using alicyclic secondary amines in the presence of sulphur (Scheme 2, Table III).

The pyrimidones **2a-d** were also prepared in very good yield in two steps from amidines **7a-d**. Condensation of amidines **7a-d** with diethyl ethoxymethylene malonate in ethanol at reflux afforded diesters **7f-i**. The formation of pyrimidones **2a-d** was best achieved using sodium ethoxide in ethanol at room temperature in the case of diester **7f** and with Dowtherm A at 270-280° for other aryl-substituted diesters **7g-i** (Scheme 1, Table IV).

The biological properties exhibited by some of the derivatives will be the subject of future communications.

EXPERIMENTAL

General.

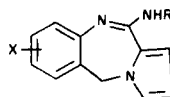
All experiments, with the exception of those in which water is used as solvents, were carried out under nitrogen. The following solvents were distilled prior to use: 1,2-dimethoxyethane and tetrahydrofuran (from sodium metal), *N,N*-dimethylformamide (from calcium hydride) and toluene was stored over sieves (Linde, 4a). Commercial starting compounds were used without further purification. Elemental microanalyses were carried out in the analytical department of this laboratory. The ir spectra were done on a Perkin-Elmer diffraction grating instrument and the uv spectra were recorded on a Unicam spectrophotometer. The melting points were taken on a Thomas-Hoover apparatus and are uncorrected. The nmr spectra were recorded on a Varian CFT 20 apparatus and mass spectra on a Hitachi RMU-60 spectrometer. Organic extracts were dried over anhydrous magnesium sulfate and solvents were always removed under vacuum. Merck silica gel 60 (70-230) was used for column chromatography unless otherwise stated. All new compounds gave satisfactory mass spectra. Thin layer chromatography (tlc) was carried out on silica gel plates using methanol-chloroform combinations in varying proportions. The chromatograms were developed in an iodine chamber.

General Procedure for Preparing *N*-Nitrobenzyl-2-pyrrolocarbonitriles (**5a-d**, Table 1).

Sodium hydride (50% mineral dispersion, 15.50 g, 323 mmoles) was added in small portions to a solution of 2-pyrrolocarbonitrile (29.00 g, 318 mmoles) in dry DMF (800 ml) stirred below -30° during 30 minutes.

Table II

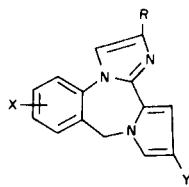
Pyrrolo[2,1-*c*][1,4]benzodiazepines



Compound No.	X	R	Mp °C	Recrystallization Solvent	Yield %	Formula	Analysis %		
							C	H	N
7a	H	H	177-178	Dichloromethane-hexane	54	C ₁₂ H ₁₁ N ₃ 197.23	lit [7] mp 179-181°		
7b	7-Cl	H	205-206	Ethyl acetate-hexane	61 [a]	C ₁₂ H ₁₀ ClN ₃ 231.68	lit [7] mp 206-208°		
7c	8-Cl	H	244-245	Ethyl acetate-hexane	71	C ₁₂ H ₁₀ ClN ₃ 231.68	lit [7] mp 245-248°		
7d	8-CH ₃	H	224-225	Ethyl acetate-hexane	46	C ₁₃ H ₁₃ N ₃ 211.25	73.94 73.63	6.20 6.22	19.90 19.89
7e	H	CH ₂ CH(OCH ₃) ₂	132-132.5	Cyclohexane-hexane	83	C ₁₆ H ₁₉ N ₃ O ₂ 285.34	67.34 67.11	6.71 6.69	14.73 14.40
7f	H	CH=C(CO ₂ C ₂ H ₅) ₂	129-130	Ether-hexane	67	C ₂₀ H ₂₁ N ₃ O ₄ 367.39	65.38 65.28	5.76 5.79	11.44 11.36
7g	7-Cl	CH=C(CO ₂ C ₂ H ₅) ₂	191-192	Ethyl acetate-hexane	79	C ₂₀ H ₂₀ ClN ₃ O ₄ 401.84	59.78 59.42	5.02 5.02	10.46 10.37
7h	8-Cl	CH=C(CO ₂ C ₂ H ₅) ₂	172-173	Dichloromethane-hexane	88	C ₂₀ H ₂₀ ClN ₃ O ₄ 401.84	59.78 59.40	5.02 5.06	10.46 10.31
7i	7-CH ₃	CH=C(CO ₂ C ₂ H ₅) ₂	139-140	Ethyl acetate-hexane	57	C ₂₁ H ₂₃ N ₃ O ₄ 381.41	66.13 66.09	6.08 6.02	11.02 11.04

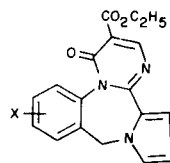
[a] 10% yield reported [7].

Table III
9*H*-Imidazo[1,2-*a*]pyrrolo[2,1-*c*][1,4]benzodiazepines



Compound No.	X	Y	R	Mp °C	Recrystallization Solvent	Yield %	Formula	Analyses, %		
								C	H	N
1a	H	H	CO ₂ C ₂ H ₅	164-165	Toluene-ether	68	C ₁₇ H ₁₅ N ₃ O ₂ 293.31	69.61 69.40	5.15 5.18	14.33 14.31
1b	6-Cl	H	CO ₂ C ₂ H ₅	209-210	Ethyl acetate-hexane	85	C ₁₇ H ₁₄ ClN ₃ O ₂ 327.76	62.29 61.90	4.30 4.12	12.82 13.19
1c	7-Cl	H	CO ₂ C ₂ H ₅	234-235	Benzene-hexane	46	C ₁₇ H ₁₄ ClN ₃ O ₂ 327.76	62.29 62.18	4.30 4.32	12.82 12.76
1d	7-CH ₃	H	CO ₂ C ₂ H ₅	187-188	Ether-hexane	77	C ₁₈ H ₁₇ N ₃ O ₂ 307.34	53.21 53.27	4.96 4.98	10.34 10.26
1e	H	H	H	202-203	Benzene-hexane	90	C ₁₄ H ₁₁ N ₃ 221.25	75.99 76.02	5.01 5.09	18.99 19.01
1f	H	CHO	H	203-205	Toluene-hexane	90	C ₁₅ H ₁₁ N ₃ O 249.26	72.27 72.08	4.45 4.51	16.86 16.77
1g	H	CHO	CO ₂ C ₂ H ₅	198-199	Toluene-hexane	16	C ₁₈ H ₁₅ N ₂ O ₃ 321.32	67.27 67.08	4.71 4.78	13.08 13.01
1h	H	pyrrolidinylthio-oxomethyl	H	165-166	Toluene-hexane	49	C ₁₉ H ₁₈ N ₄ S 334.43	68.23 68.17	5.42 5.61	16.75 16.38
1i	H	morpholinylthio-oxomethyl	H	210-211	Toluene-hexane	48	C ₁₉ H ₁₈ N ₄ OS 350.43	65.12 65.11	5.18 5.31	15.99 16.00
1j	H	thiomorpholinylthio-oxomethyl	H	202-203	Benzene-hexane	45	C ₁₉ H ₁₈ N ₄ S ₂ 366.49	62.26 62.00	4.95 5.01	15.29 15.12
1k	H	4-methylpiperazinythio-oxomethyl	H	211-212	Acetonitrile-ether	42	C ₂₀ H ₂₁ N ₅ S 363.48	66.08 66.08	5.82 5.86	19.27 19.33
1l	H	4-(4-fluorophenyl)piperazinythio-oxomethyl	H	275-276	DMF-ether	35	C ₂₅ H ₂₅ Cl ₃ FN ₅ S 552.93	54.30 54.70	4.55 4.53	12.66 13.00
1m	H	morpholinylthio-oxomethyl	CO ₂ C ₂ H ₅	232-233	Benzene-hexane	53	C ₂₂ H ₂₂ N ₄ O ₃ S 422.50	62.54 62.57	5.25 5.38	13.26 13.23

Table IV
10*H*-Pyrimido[1,2-*a*]pyrrolo[2,1-*c*]benzodiazepine-3-carboxylic Acid Ethyl Ester



Compound No.	X	Mp °C	Recrystallization Solvent	Yield %	Formula	Analyses %		
						C	H	N
2a	H	214-215	Acetonitrile	86	C ₁₈ H ₁₅ N ₃ O ₃ 321.22	67.28 67.26	4.71 4.79	13.08 13.13
2b	7-Cl	247-248	Toluene-hexane	68	C ₁₈ H ₁₄ ClN ₃ O ₃ 355.77	60.76 60.43	3.97 4.12	11.81 11.63
2c	8-Cl	209-210	Ethyl acetate-toluene	84	C ₁₈ H ₁₄ ClN ₃ O ₃ 355.77	60.76 60.74	3.97 4.05	11.81 11.77
2d	8-CH ₃	207-208	Ethyl acetate-hexane	84	C ₁₉ H ₁₇ N ₃ O ₃ 335.35	68.05 68.15	5.11 5.19	12.53 12.46

After the reaction, a solution of 5-methyl-2-nitrobenzyl chloride (50.00 g, 270 mmoles) in DMF (200 ml) was added dropwise to the reaction mixture. The internal temperature of the mixture was allowed to attain room temperature within an hour. The dark solution was then poured into ice-water containing dilute hydrochloric acid. The crude tan precipitate was filtered, air-dried and recrystallized from diethylether-hexane at 0° to afford a crop of white crystals (53.37 g, 70%) of **5d**, of mp 97-98°; ir (nujol): ν max 2200, 1520, 1345 cm^{-1} ; uv (methanol): λ max 252 (ϵ 15600), 223 (ϵ 14700); nmr (deuteriochloroform): δ 2.35 (s, 3H, CH₃), 5.62-6.87 (m, 4H, ArH), 8.04 (d, J = 8.5 Hz, 1H, ArH).

Procedure for Preparing *N*-Aminobenzyl-2-pyrrolicarbonitriles (**6a-d**, Table I).

1-(5-Methyl-2-nitrobenzyl)-2-pyrrolicarbonitrile (**5d**) (7.70 g, 31.92 mmoles) was reduced on 10% palladium on charcoal in methanol (200 ml) at atmospheric pressure under hydrogen for 3 hours at room temperature. The catalyst was filtered off and concentrated. The residue was dissolved in methylene chloride, treated with Norite and the dried solution concentrated. The crude solid thus obtained was filtered through a short silica gel column using methylene chloride. The main fraction was recrystallized from cyclohexane to yield 6.30 g (93%) of **6d** as off-white crystals of mp 111-112°; ir (nujol): ν max 3380, 3340, 3240 cm^{-1} ; uv (methanol): λ max 295 (ϵ 2410), 242 (ϵ 17300); nmr (deuteriochloroform): δ 2.19 (s, 3H, CH₃), 3.40 (broad, 2H, NH₂), 5.05 (s, 2H, CH₂N), 6.60 (m, 6H, ArH).

Procedure for Preparing 11-Amino-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepines (**7a-d**, Table II).

Benzyl trimethylammonium hydroxide (40% in methanol, 0.6 ml) was added to a stirred solution of 1-(5-methyl-2-aminobenzyl)-2-pyrrolicarbonitrile (**6d**) (1.00 g, 4.73 mmoles) in toluene (15 ml) at reflux for 3 hours. The solution was decanted, cooled, crystals collected by filtration and recrystallized from ethyl acetate-hexane to afford 460 mg (46%) of **7d** of mp 224-225°; ir (nujol): ν max 3420, 3290, 3060, 1575, 1520 cm^{-1} ; uv (methanol): λ max 296 (ϵ 11800), 284 (ϵ 12300), 267 (ϵ 12400); nmr (DMSO-*d*₆): δ 2.19 (s, 3H, CH₃), 4.85 (s, 2H, CH₂), 6.01 (m, 1H, ArH), 6.29 (s, 2H, NH₂), 6.40 (m, 1H, ArH), 6.89 (m, 4H, ArH).

[5*H*-Pyrrolo[2,1-*c*][1,4]benzodiazepin-11-yl]amino]acetaldehyde Dimethylacetal (**7e**, Table II).

A mixture of 11-amino-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine (**7a**) (2.00 g, 10.1 mmoles) and aminoacetaldehyde dimethylacetal (8.8 ml) was stirred in toluene (50 ml) at reflux for 3 hours in the presence of ammonium chloride (200 mg, 3.7 mmoles). The precipitate which formed redissolved after a while; the resulting brown solution was then cooled, washed with dilute sodium hydroxide, brine, dried and concentrated. The oily residue was crystallized from cyclohexane-hexane to afford tan crystals (2.41 g, 83%) of **7e** of mp 132-132.5°; ir (chloroform): ν max 3430, 1600, 1580, 1560, 1515, 1120 cm^{-1} ; uv (methanol): λ max 261 (ϵ 15600) with shoulders at 285 and 226; nmr (deuteriochloroform): δ 3.41 (s, 6H, CH₃O), 3.65 (t, J = 5.5 Hz, 2H, CH₂), 4.55 (t, J = 5.5 Hz, 1H, CH), 4.82 (s, 2H, CH₂), 4.88 (broad, 1H, NH), 6.67 (m, 7H, ArH).

Procedure for Preparing [(5*H*-Pyrrolo[2,1-*c*][1,4]benzodiazepin-11-yl)amino]methylenepranedioic Acid Diethyl Esters (**7f-i**, Table II).

11-Amino-7-chloro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine (**7b**) (2.70 g, 11.65 mmoles) was stirred in diethyl ethoxy methylenemalonate (35 ml) on a steam-bath for 30 minutes. The mixture was cooled, saturated with hexane to yield a pale yellow powder. Recrystallization from ethyl acetate-hexane gave 3.80 g (79%) of **7g**, mp 191-192°; ir (nujol): ν max 3280, 1723, 1655 cm^{-1} ; nmr (deuteriochloroform): δ 1.34 and 1.36 (t, J₁ = J₂ = 7 Hz, 6H, CH₃), 4.25 and 4.28 (q, J₁ = J₂ = 7 Hz, 4H, CO₂CH₂), 4.87 (s, 2H, CH₂), 6.20 (dd, J₁ = 4 Hz, J₂ = 3 Hz, 1H, pyrrole), 6.65 (dd, J₁ = 4 Hz, J₂ = 3 Hz, 1H, pyrrole), 6.80 (m, 1H, pyrrole), 7.15 (m, 3H, ArH), 9.02 and 9.17 (s, 1H, NCH=C).

Procedure for Preparing 9*H*-Imidazo[1,2-*a*]pyrrolo[2,1-*c*][1,4]benzodiazepine-2-carboxylic Acid, Ethyl Esters (**1a-d**, Table III).

(A) 11-Amino-7-methyl-10-(3-ethoxy-2,3-dioxopropyl)-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepinium Bromide (**8**, X = 7-CH₃).

Amidine **7d** (2.00 g, 9.50 mmoles) and ethyl bromopyruvate (1.4 ml) were stirred in dry tetrahydrofuran (100 ml) at room temperature for 3 hours. The white precipitate was filtered and dried to yield 2.14 g (56%) of the title compound of mp 176-177°.

Anal. Calcd. for C₁₈H₂₀BrN₃O₃: C, 53.21; H, 4.96; N, 10.34. Found: C, 53.27; H, 4.98; N, 10.26.

(B) 7-Methyl-9*H*-imidazo[1,2-*a*]pyrrolo[2,1-*c*][1,4]benzodiazepine-2-carboxylic Acid Ethyl Ester (**1d**).

The quaternary bromide **8** (2.50 g, 6.15 mmoles) was stirred in ethanol (100 ml) at reflux for 1 hour. The solvent was removed, methylene chloride added and the corresponding free base of **1d** was generated with aqueous sodium carbonate. The organic phase was washed with brine, dried and concentrated to give a residual solid which recrystallized readily from diethyl ether-hexane as white crystals (1.44 g, 77%) of mp 187-188°; ir (nujol): ν max 1710 cm^{-1} ; uv (methanol): λ max 280 (ϵ 16000), 241 (ϵ 24200); nmr (deuteriochloroform): δ 1.41 (t, J = 7 Hz, 3H, CH₃), 2.35 (s, 3H, CH₃), 4.39 (q, J = 7 Hz, 2H, CH₂OCO), 4.95 (s, 2H, CH₂N), 6.92 (m, 7H, ArH).

9*H*-Imidazo[1,2-*a*]pyrrolo[2,1-*c*][1,4]benzodiazepine (**1e**, Table III).

[(5*H*-Pyrrolo[2,1-*c*][1,4]benzodiazepine-11-yl)amino]acetaldehyde dimethylacetal (**7e**) (6.00 g, 21.0 mmoles) was stirred in 2*N* hydrochloric acid (200 ml) at reflux for 3 hours. The cold mixture was basified using 10% sodium hydroxide and extracted with chloroform. The combined extracts were washed with brine, dried and concentrated to afford 4.16 g (90%) of tan crystals from benzene-hexane of mp 202-203°; ir (chloroform): ν max 1600, 1585, 1505 cm^{-1} ; uv (methanol): λ max 296 (ϵ 8960), 234 (ϵ 17680); nmr (deuteriochloroform): δ 4.95 (s, 2H, CH₂N), 6.15 (t, J = 3 Hz, 1H, ArH), 6.71 (m, 2H, ArH), 7.32 (m, 6H, ArH).

Procedure for Preparing Aldehydes (**1f-g**, Table III).

A mixture of 9*H*-imidazo[1,2-*a*]pyrrolo[2,1-*c*][1,4]benzodiazepine (**1e**) (8.00 g, 36.1 mmoles) and phosphoryl chloride (10.40 g, 6.32 ml, 67.5 mmoles) was stirred in dry DMF (120 ml) at 120° for 2 hours. The reaction mixture was poured in water (800 ml) and extracted with several portions of chloroform. The combined extracts were washed with water, brine and concentrated to yield a crop of **1f** of tan crystals (3.57 g, 90%) mp 203-205° from toluene-hexane; ir (nujol): ν max 1670 cm^{-1} ; uv (methanol): λ max 327 (ϵ 19650), 250 (ϵ 14100), 223 (ϵ 15800); nmr (DMSO-*d*₆): δ 5.65 (s, 2H, CH₂N), 7.30 (m, 8H, ArH), 9.61 (s, 1H, CHO).

Procedure for Preparing Thioamides (**1h-m**, Table III).

A mixture of 9*H*-imidazo[1,2-*a*]pyrrolo[2,1-*c*][1,4]benzodiazepine-12-carboxaldehyde (**1f**) (3.30 g, 13.3 mmoles), sulphur (1.52 g, 4.74 mg) and morpholine (25.4 ml) was heated with steam for 2 hours. The black mixture was then refluxed in ethanol (50 ml) for 30 minutes. The yellow precipitate obtained upon cooling of the reaction mixture, was recrystallized from toluene-hexane to give **1i** as a crop of yellow crystals (2.25 g, 48%) mp 210-211°; ir (nujol): ν max 1605, 1595, 1575, 1503 cm^{-1} ; uv (methanol): λ max 299 (ϵ 19300); nmr (deuteriochloroform): δ 3.75 (t, J = 5 Hz, 4H, CH₂O), 4.12 (m, 4H, CH₂NCS), 5.20 (m, 2H, CH₂N), 6.12 (s, J = 4 Hz, 1H, ArH), 6.70 (d, J = 4 Hz, 1H, ArH), 7.30 (m, 5H, ArH), 7.70 (m, 1H, ArH).

Procedures for Preparing 4-Oxo-10*H*-pyrimido[1,2-*a*]pyrrolo[2,1-*c*][1,4]benzodiazepine-3-carboxylic Acid Ethyl Ester (**2a-d**, Table IV).

(a) Using Sodium Ethoxide.

[(5*H*-Pyrrolo[2,1-*c*][1,4]benzodiazepin-11-yl)amino]methylenepranedioic acid diethyl ester (**7f**) (6.90 g, 18.8 mmoles) was stirred in warm ethanol in the presence of a catalytic amount of sodium ethoxide. After an hour, the yellow precipitate was collected by filtration and recrystallized from acetonitrile to afford **2a** (5.20 g, 86%) of mp 214-215°; ir (nujol): ν max 1735, 1690 cm^{-1} ; uv (methanol): λ max 269 (ϵ 4375) and shoulder at 224; nmr (DMSO-*d*₆): δ 1.25 (t, J = 7 Hz, 3H, CH₃), 4.21 (q, J = 7 Hz, 2H, CH₂OCO), 5.12 and 5.37 (d, J = 13 Hz, 2H, CH₂), 7.33 (m, 8H, ArH).

(b) Using Dowtherm A.

[(7-Methyl-5H-pyrrolo[2,1-c][1,4]benzodiazepin-11-yl)amino]methylene-propanedioic acid, diethyl ester (**7i**) (2.50 g, 6.55 mmoles) was dissolved in Dowtherm A (20 ml) and stirred in a preheated metal bath between 268-278° for 2 hours. The dark mixture was cooled and diluted in hexane to yield a deposit (2.24 g) which was purified by filtration through a silica gel column using a 7:1 methylenechloride-ethyl acetate solvent combination. The main fraction was concentrated and the residual solid was recrystallized from ethyl acetate-hexane to yield 1.84 g (84%) of crystals of mp 207-208° of ester **2d**; ir (chloroform): ν max 1700 cm^{-1} ; uv (methanol): λ max 376 (ϵ 25000); nmr (deuteriochloroform): δ 1.37 (t, J = 7 Hz, 3H, CH₃), 2.35 (s, 3H, CH₃), 4.35 (q, J = 7 Hz, 2H, CH₂), 5.03 (d, J = 14 Hz, 2H, CH₂N), 6.19 (m, 1H, ArH), 7.15 (m, 5H, ArH), 8.69 (s, 1H, NCH=C).

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