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Benzodiazepines. VII.[1] Pyrazino[1,2-*a*]indole-1(2*H*)-ones and Their Conversion to 2,3-Dihydro-1*H*-1,4-benzodiazepines

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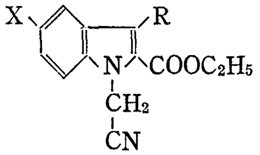
A new synthetic route for the preparation of 2,3-dihydro-1*H*-1,4-benzodiazepines (**6**) is described. It consists of performing successively N-cyanomethylation of ethyl indole-2-carboxylates (**1**), reduction of cyano group, oxidation of 1-aminoethylindole derivatives (**3** or **4**) and finally hydrolysis of 2,3-piperazinediones (**5**). In an alternative synthesis of the key intermediate **4a**, intramolecular alkylation of N-(2-chloroethyl)indole-2-carboxamide (**11**) gave a mixture of **4a** and 2-oxazolinylindole (**12**).

In the preceding papers[3] from our laboratories it has been reported that 2-aminomethylindoles can be oxidized to the corresponding 1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones. We have now examined the oxidation of 1-aminoethyl-substituted indoles.

Ethyl indole-2-carboxylates bearing aminoethyl group in position 1 were prepared from the unsubstituted esters (**1**) in two steps. In the first step, compounds (**1**) were alkylated *via* the sodio derivative with chloroacetonitrile to give the 1-cyanomethylindoles (**2**). In the second step, compounds (**2**) were converted to 1-aminoethylindoles (**3**) by selective reduction of the nitrile group without affecting the ester group or the nitro group with diborane or Raney nickel hydrogenation. The compound (**3**) formed initially cyclized partially during

Table I



Compd. No.	R	X	mp (°C) (Crystd. from[a])	Yield (%)	Formula		Analysis C	H	N	Cl, Br
2a	C_6H_5	Cl	126.5—127 (b+h)	99.0	$C_{19}H_{15}O_2N_2Cl$	Calcd.	67.36	4.46	8.27	10.47
						Found	67.57	4.22	7.96	10.64
2b	C_6H_5	NO_2	153 —155 (EtOH)	91.3	$C_{19}H_{15}O_4N_3$	Calcd.	65.32	4.33	12.03	
						Found	65.32	4.31	11.96	
2c		Cl	154 —156 (EtOH)	64.2[b]	$C_{18}H_{14}O_2N_3Cl$	Calcd.	63.63	4.15	12.37	10.44
						Found	63.65	4.21	12.31	10.38
2d		Br	170 —171 (EtOH)	68.5[b]	$C_{18}H_{14}O_2N_3Br$	Calcd.	56.26	3.67	10.94	20.80
						Found	56.23	3.61	10.89	20.66

a) b=benzene; h=hexane
b) Value obtained is from a single experiment and no attempts have been made to obtain optimal yield.

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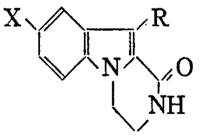
[1] Part VI: K. Ishizumi, S. Inaba, and H. Yamamoto, *Chem. Pharm. Bull.* (Tokyo), **20**, 592, (1972).

[2] Location: *2-1, Takatsukasa-4-chome, Takarazuka-shi, Hyogo.*

[3] *a*) H. Yamamoto, S. Inaba, T. Hirohashi, and K. Ishizumi, *Chem. Ber.*, **101**, 4245 (1968); *b*) S. Inaba, T. Hirohashi, and H. Yamamoto, *Chem. Pharm. Bull.* (Tokyo), **17**, 1263 (1969); *c*) S. Ianba, K. Ishizumi, and H. Yamamoto *Chem. Pharm. Bull.* (Tokyo), **19**, 263 (1971); *d*) S. Inaba, K. Ishizumi, K. Mori, and H. Yamamoto, *Chem. Pharm. Bull.* (Tokyo), **19**, 722 (1971).

Table II



Compd. No.	R	X	mp (°C) (Crystd. from[a])	Reagent	Yield[b] (%)	Formula		Analysis C	H	N	Cl, Br
4a	C_6H_5	Cl	244.5—245 (EtOH)	H_2/Ni BH_3	42.8 57.3	$C_{17}H_{13}ON_2Cl$	Calcd. Found	68.80 68.52	4.41 4.27	9.44 9.39	11.95 12.01
4b	C_6H_5	NO_2	280 —285[c] (EtOH+b)	BH_3	56.2	$C_{17}H_{13}O_3N_3$	Calcd. Found	66.44 66.33	4.26 4.18	13.68 13.56	
4c		Cl	280 —282.5 (EtOH)	H_2/Ni	46.9[d]	$C_{16}H_{12}ON_3Cl$	Calcd. Found	64.54 64.32	4.06 4.06	14.11 14.07	11.91 11.63
4d		Br	264 —266 (EtOH)	H_2/Ni	48.8[d]	$C_{16}H_{12}ON_3Br$	Calcd. Found	56.16 56.91	3.53 3.66	12.28 11.70	23.35 22.43

[a] b=benzene; [b] yield from 2; [c] decomposition point
[d] Value obtained is from a single experiment and no attempts have been made to obtain optimal yield.

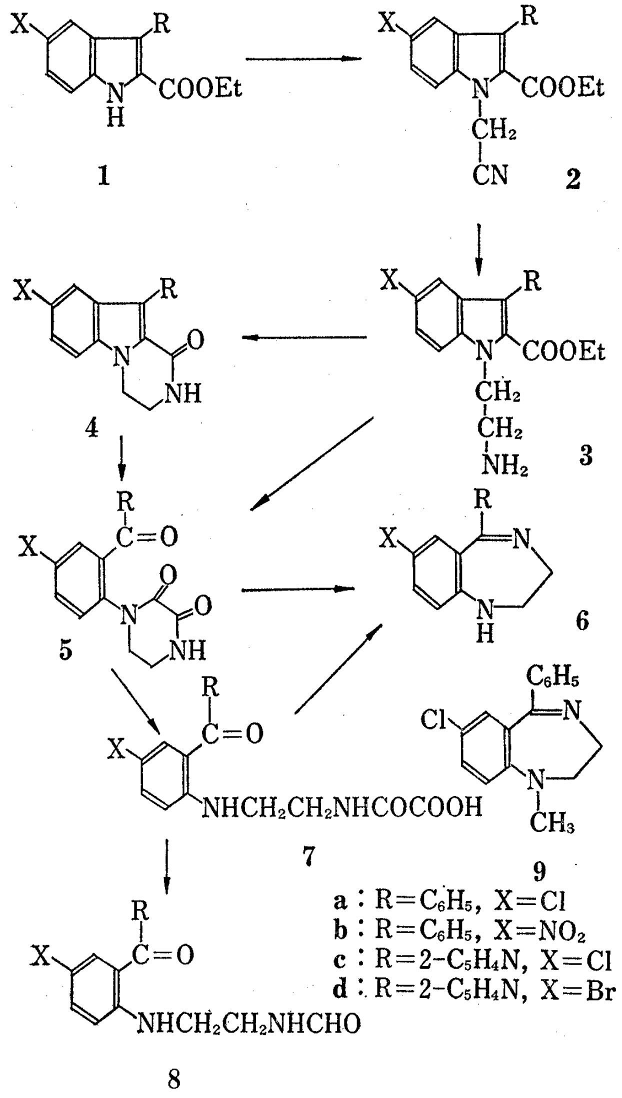


Chart 1

the isolation procedure to the corresponding pyrazino[1,2-*a*]indole-1(2*H*)-one (**4**). Cyclization was well effected by refluxing in carbon tetrachloride. 1-Aminoethylindole (**3a**) was isolated as the hydrochloride. The structures of compounds (**3** and **4**) were supported by elemental analyses and the infrared (IR), nuclear magnetic resonance (NMR) and mass spectra.

In an alternate synthesis of **4a**, intramolecular cyclization of 5-chloro-N-(2-chloroethyl)-3-phenylindole-2-carboxamide (**11**) was performed. Compound (**11**) was prepared from the ester (**1a**) by heating with an excess of ethanolamine, followed by treatment with thionyl chloride. Intramolecular alkylation of compound (**11**) with anhydrous potassium carbonate in dimethylformamide afforded a mixture of the expected pyrazinoindole (**4a**) (44%) and the by-product **12** (32%) which was shown to be isomeric with compound (**4a**) by elemental and mass analyses. The two compounds were readily separated by making use of the solubility of compound (**12**) in carbon tetrachloride in which compound (**4a**) was insoluble. The compound (**12**) was prepared in almost quantitative yield by treatment of compound (**11**) with alcoholic sodium hydroxide. For this compound the oxazoline (**12**) was the more

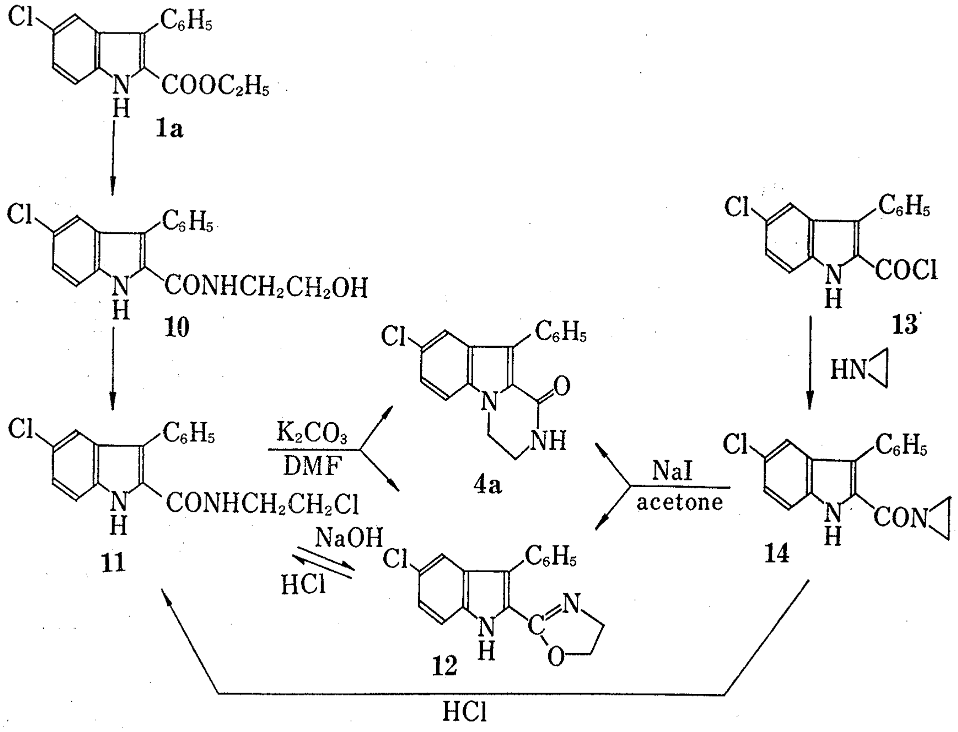


Chart 2

likely one of the two possible structures **12** and **14** since similar cyclizations of N-2-haloethylbenzamides to phenyl-2-oxazolines are described in the literature.[4] Independent synthesis of **14** from aziridine by acylation with the acid chloride (**13**) ruled out the conversion of compound (**11**) to compound (**14**) and a comparison of the spectral properties of **4a, 12** and **14** supported the structural assignment (Table III, IV and V).

Table III. IR Spectra of Compounds (**4a, 12** and **14**)

Compd. No.	ν_{N-H} (cm^{-1}) in CHCl$_3$$^{a)}$	ν_{N-H} (cm^{-1}) in Nujol	$\nu_{C=O}$, $\nu_{C=N}$ (cm^{-1}) in CHCl$_3$	$\nu_{C=O}$, $\nu_{C=N}$ (cm^{-1}) in Nujol
4a	3419	3180, 3050	1674	1675
12	3447	3120 (braod)	1643	1640
14	3444	3290	1643	1640

a) 0.2 w/v % in CHCl$_3$

Table IV. NMR Spectra of Compounds (**4a, 12** and **14**) in C_5D_5N

Compd. No.	-CH$_2$CH$_2$- (4H) δ	Aromatic H (8H, m) δ	NH (1H, s) δ
4a	3.50—3.76 (2H, m), 4.05—4.25 (2H, m)	7.40—8.05	8.95
12	3.70—4.20 (m)	7.26—7.86	13.12
14	1.96 (s)	7.30—7.83	8.52

Compound (**12**) could not be easily distinguished from compound (**14**) by a comparison of the IR spectra since compounds (**12** and **14**) have both the strong absorption at 1640 cm^{-1}

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4) *a)* M.T. Leffler and R. Adams, *J. Am. Chem. Soc.*, **59**, 2252 (1937); *b)* A.A. Goldberg and W. Kelly, *J. Chem. Soc.*, **1948**, 1919.

Table V. Mass Spectra of Compounds (**4a**, **12** and **14**)

m/e	Relative intensity 4a	12	14	*m/e*	Relative intensity 4a	12	14
296	100	39	56	216		11	
295	15	100	35	204	95	6	
268	12	4	7	203	19		
267	11			199		4	12
253		11	100	191		8	28
251		13		190	11	22	94
239	19	4		177	11	3	4
238	18	6		176	13	4	
225		2	9	164	7	7	16
224		6	9	163	11	8	20
219			11				

for the C=N group and the C=O group. The NMR and mass spectra of compounds (**4a**, **12** and **14**) exhibit characteristic differences. The NMR spectrum of **4a** shows two groups of two-proton signal centered at δ 3.68 and δ 4.15 for the two methylen groups. The four protons of the two methylen groups in compound (**12**) show the multiplet absorption centered at δ 4.0 while these protons in compound (**14**) appear as a singlet at δ 1.96. In the mass spectrum of compound (**12**) the base peak is the M-1 ion, corresponding to loss of a hydrogen atom from the oxazoline ring.5)

Further intense peaks are due to 2-(5-chloroindole) CN ion (*m/e* 251), 2-indole CN ion (*m/e* 216) and 2-indole radical ion (*m/e* 190). In contrast to compound (**12**), the base peak in the spectrum of compound (**14**) is M-C_2H_4NH ion and the fragmentation pathway is analogous to that reported for indole-2-carboxamide.5b)

It was reported6) that 1-aroylaziridines rearranged to form 2-aryl-2-oxazolines by treatment with nucleophiles such as iodide ion. Interestingly, treatment of compound (**14**) with sodium iodide in acetone resulted in the formation of a mixture of the expected oxazoline (**12**) and the pyrazinoindole (**4a**). The plausible mechanism6b) for this rearrangement is shown in Chart 3.

Compounds (**12** and **14**) were both converted to **11** by treatment with 3N hydrochloric acid.

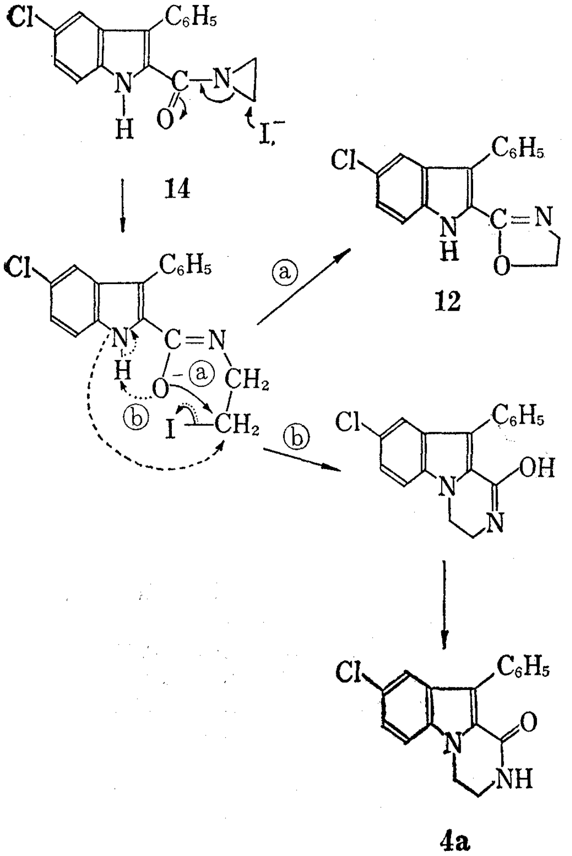

Chart 3

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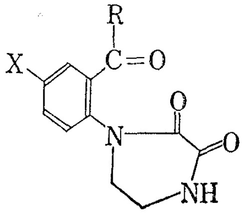
5) *a*) Q.N. Porter and J. Baldas, "General Heterocyclic Chemistry: Mass Spectrometry of Heterocyclic Compounds," ed. by A. Weissberger and E.C. Taylor, Wiley-Interscience, Inc., New York, **1971**, Chapter 10 and 13; *b*) J.C. Powers, *J. Org. Chem.*, **33**, 2044 (1968); *c*) R.T. Lundquist and A. Ruby, *Appl. Spectrosc.*, **20**, 258 (1966).

6) *a*) J.F. Bieron and F.J. Dinan, "The Chemistry of Amides," ed. by J. Zabicky, Interscience Publishers, Inc., New York, 1970, Chapter 4; *b*) H.W. Heine, M.E. Fetter, and E.M. Nicholson, *J. Am. Chem. Soc.*, **81**, 2202 (1959).

Compounds (**3a**, **4a** and **4b**) were oxidized with chromium trioxide in acetic acid to the corresponding 2,3-piperazinediones (**5**). Unfortunately it was observed that the oxidation of 3-(2-pyridyl) indoles (**4c** and **4d**) was prevented by initial formation of insoluble complex of compounds (**4**) and chromic acid. The oxidation of pyridylindoles (**4c** and **4d**) to their respective piperazinediones (**5c** and **5d**) was, however, achieved by using ozone in acetic acid as oxidant.

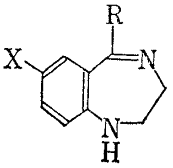
TABLE VI



Compd. No.	R	X	mp (°C) (Crystd. from[a])	Reagent	Yield[b] (%)	Formula		Analysis			
								C	H	N	Cl, Br
5a	C_6H_5	Cl	198—198.4	CrO_3	82.3	$C_{17}H_{13}O_3N_2Cl$	Calcd.	62.11	3.99	8.52	10.78
			(aq. EtOH)				Found	62.15	4.11	8.47	10.60
5b	C_6H_5	NO_2	225—228[c]	CrO_3	44.6	$C_{17}H_{13}O_5N_3$	Calcd.	60.17	3.86	12.39	
			(EtOH+b)				Found	60.15	3.76	12.25	
5c		Cl	121—123	O_3[d,e]	27.1	$C_{16}H_{12}O_3N_3Cl$	Calcd.	58.28	3.67	12.47	10.75
			(b)				Found	58.48	3.50	12.50	10.42
5d		Br	123—125[c]	O_3[d,e]	26.9	$C_{16}H_{12}O_3N_3Br$	Calcd.	51.35	3.23	11.23	21.36
			(b)				Found	51.56	3.27	11.01	21.21

a) b=benzene; b) yield from **4**; c) decomposition point
d) Value obtained is from a single experiment and no attempts have been made to obtain optimal yield.
e) Starting material was recovered.

TABLE VII[7–9]



Compd. No.	R	X	mp (°C) (Crystd. from)	Yield[a] (%)	Formula		Analysis			
							C	H	N	Cl, Br
6a	C_6H_5	Cl	173—173.5[b]	89.7	$C_{15}H_{13}N_2Cl$	Calcd.	70.17	5.10	10.91	13.81
			(EtOH)			Found	70.08	5.14	10.88	14.11
6b	C_6H_5	NO_2	209—211[c]	19.0[d]	$C_{15}H_{13}O_2N_3$	Calcd.	67.40	4.90	15.72	
			(acetone)			Found	67.42	4.89	15.62	
6c		Cl	187—188	64.0[d]	$C_{14}H_{12}N_3Cl$	Calcd.	65.24	4.70	16.30	13.76
			(EtOH)			Found	65.28	4.71	16.22	14.07
6d		Br	197—198[e]	70.8[d]	$C_{14}H_{12}N_3Cl$	Calcd.	55.64	4.00	13.91	26.45
			(EtOH)			Found	55.69	4.15	13.80	26.46

a) yield from **5** b) Lit.[7] mp 172—174° c) Lit.[8] mp 210—212°
d) Value obtained is from a single experiment and no attempts have been made to obtain optimal yield.
e) Lit.[9] mp 195—197°

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7) L.H. Sternbach, E. Reeder, and G.A. Archer, *J. Org. Chem.*, **28**, 2456 (1963).

8) L.H. Sternbach, G.A. Archer, and E. Reeder, *J. Org. Chem.*, **28**, 3013 (1963).

9) G.A. Archer, A. Stempel, S.S. Ho, and L.H. Sternbach, *J. Chem. Soc.* (*C*), **1966**, 1031.

Alkaline hydrolysis of compounds (**5**) gave the expected benzodiazepines (**6**). The compound (**6a**) was shown to be identical with an authentic sample prepared from the corresponding benzodiazepin-2-one by lithium aluminium hydride reduction.[7] When the reaction was interrupted after a short period, [2-(2-benzoyl-4-chloroanilino)ethyl]oxamic acid (**7a**) could be isolated. The mass spectrum of compound (**7a**) which exhibits the weak molecular ion (*m/e* 346) and a M-44 (CO_2) peak (*m/e* 302), as well as the IR spectrum with two carbonyl bands at 1743 and 1716 cm^{-1} indicates the presence of an oxalyl group. The NMR spectrum shows the position of the oxalyl group by the appearance of the two exchangeable protons attached to the nitrogen atoms at δ 8.35 and δ 8.95.

Decarboxylation of compound (**7a**) by heating in tetraline afforded N-[2-(2-benzoyl-4-chloroanilino)ethyl] formamide (**8a**), whose mass spectrum was closely similar to that of compound (**7a**).

L.H. Sternbach, *et al.*[7] described that compound (**6a**) was methylated with sodium hydride and methyl iodide in dimethylformamide to give the 1-methyl derivative (**9**) in poor yield, but in our hands only the starting material was recovered. However, it was found that use of phenyllithium as condensing agent gave the desired product (**9**) in a high yield. The first evidence of compound (**9**) was provided by the NMR spectrum which shows a three-proton singlet at δ 2.72 for N-CH_3 group. The structural assignment was further confirmed by an alternate preparation from N-[2-(4-chloroanilino)ethyl]benzamide by H.H. Kaegi's method.[10]

Experimental

All melting points were determined in open capillary tubes and are uncorrected. IR spectra were measured on a Hitachi Model EPI-G3 spectrophotometer, and NMR spectra on a Varian T-60 instrument using tetramethylsilane as an internal standard. Following abbreviations are used for the representation of NMR data: s=singlet, d=doublet, t=triplet, q=quartet, and m=multiplet. Mass spectra were determined on a Hitachi RMU-6L instrument with the direct sample inlet system; ionizing potential at 70 eV. All solvents used for extraction were dried over anhydrous Na_2SO_4 after extraction and evaporated on a rotary evaporator under water aspirator pressure.

Ethyl 5-Chloro-3-(2-pyridyl)indole-2-carboxylate (1c)——To a solution of 41.8 g of ethyl 2-pyridylpyruvate 1-oxide[11] in 150 ml of chloroform was added 27.5 g of phosphorus trichloride. The mixture was stirred at 20° for 30 min and poured into ice water. The aqueous layer separated, was made basic with ammonia water and extracted with ether. The ethereal layer was washed with water, dried and evaporated to leave 13 g of solid product. Recrystallization from petroleumbenzin-ethanol gave ethyl 2-pyridylpyruvate as slightly yellow crystals, mp 83—83.5° (lit.[12] 82.5—83.5°).

To a mixture of 5.0 g of ethyl 2-pyridylpyruvate and 4.7 g of *p*-chlorophenylhydrazine in 20 ml of acetic acid was added 5 ml of conc. H_2SO_4. The mixture was stirred under reflux for 1 hr. After cooling, the reaction mixture was diluted with ice water, made basic with ammonia water and extracted with chloroform. The organic layer was washed with water, dried and evaporated, and the residue was crystallized from ethanol–benzene to give 2.9 g (37.3%) of **1c**. Recrystallization from aq. ethanol afforded colorless needles, mp 155—155.5°. *Anal.* Calcd. for $C_{16}H_{13}O_2N_2Cl$: C, 63.90; H, 4.36; N, 9.32; Cl, 11.79. Found: C, 63.78; H, 4.34; N, 9.19; Cl, 11.45.

Ethyl 5-Bromo-3-(2-pyridyl)indole-2-carboxylate (1d)——The compound (**1d**) was prepared as above in 79.1% yield from *p*-bromophenylhydrazine hydrochloride. Recrystallization from ethanol gave colorless needles, mp 151—152°. *Anal.* Calcd. for $C_{16}H_{13}O_2N_2Br$: C, 55.67; H, 3.79; N, 8.12; Br, 23.15. Found: C, 55.43; H, 3.63; N, 8.00; Br, 22.88.

Ethyl 5-Chloro-1-cyanomethyl-3-phenylindole-2-carboxylate (2a)——To a stirred suspension of 3.8 g of 69.6% sodium hydride oil dispersion in 30 ml of dimethylformamide (DMF) was added a solution of 30 g of **1a** in 90 ml of DMF at 25—30°. After stirring for 1 hr, 8.67 g of chloroacetonitrile was added dropwise, and the mixture was stirred at 20° for 2 hr. After addition of 30 ml of hexane, the reaction mixture was poured into 600 ml of ice water and stirred at room temperature for 1 hr. The resultant precipitate was collected by filtration, washed with water and dried to give 33.5 g (99%) of **2a**, mp 113.5—118°. Recrystallizations from benzene–hexane gave pure **2a**, mp 126.5—127°.

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10) H.H. Kaegi, *J. Labelled Compds*, **4**, 363 (1968).

11) R. Adams and S. Miyano, *J. Am. Chem. Soc.*, **76**, 3168, (1954).

12) E.D. Amstutz and M.M. Besso, *J. Org. Chem.*, **25**, 1687 (1960).

Other compounds (**2b**, **2c**, and **2d**) which were listed in Table I were prepared in a similar manner.

Ethyl 1-Aminoethyl-5-chloro-3-phenylindole-2-carboxylate (3a)——To a stirred suspension of 2.52 g of sodium borohydride in 40 ml of tetrahydrofurane (THF) was added dropwise a solution of 10.24 g of boron trifluoride etherate in 20 ml of THF below 20° over a period of 15 min. After 10 min, a solution of **2a** in 60 ml of THF was added dropwise over a period of 20 min, and the mixture was stirred at room temperature for 4 hr. The excess hydride in the reaction mixture was destroyed by adding 5.6 ml of 10% aq. HCl under cooling. After evaporation of THF, 100 ml of dichloromethane was added, followed by 36 ml of conc. HCl. After stirring overnight at room temperature, the precipitate was collected by filtration, washed with water followed by dichloromethane and dried to give 14.6 g (64%) of the crude hydrochloride of **3a**, mp 195—197° (decomp.). An analytical sample was obtained as colorless needles, mp 205—207° (decomp.) after treatment with activated charcoal followed by two recrystallizations from ethanol. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1690 (CO). NMR (DMSO-d_6) δ: 1.03 (3H, t, $J=7$ cps, CH_3), 3.29 (2H, t, $J=7$ cps, $CH_2C\underline{H}_2$-NH_2), 4.19 (2H, q, $J=7$ cps, CH_2Me), 4.88 (2H, t, $J=7$ cps, $C\underline{H}_2CH_2NH_2$), 7.38 (7H, s, C_6H_5 and indole ring H) and 8.05 (1H, d, $J=9$ cps, indole ring H). Mass Spectrum *m/e*: 342 (29%, M$^+$), 313 (100), 296 (30), 284 (38), 254 (21), 204 (38) and 190 (32). *Anal.* Calcd. for $C_{19}H_{20}O_2N_2Cl_2$: C, 60.17; H, 5.31; N, 7.39; Cl, 18.69. Found: C, 60.24; H, 5.59; N, 7.40; Cl, 18.37.

8-Chloro-3,4-dihydro-10-phenyl-pyrazino[1,2-*a*]indole-1(2*H*)-one (4a)——a) Raney Ni Hydrogenation of **2a**: A solution of 69.5 g of **2a** in 200 ml of THF was shaken with hydrogen at room temperature in the presence of Raney nickel catalyst which was prepared from 78 g of Raney nickel alloy by heating with 460 g of 25% aq. NaOH at 100° for 1 hr. After hydrogen uptake ceased, the solution was filtered, the catalyst was washed with 200 ml of THF, and the filtrates were combined and evaporated. The residue was dissolved in 150 ml of carbon tetrachloride and the solution was allowed stand overnight at room temperature. The resultant precipitate was collected by filtration, washed with 50 ml of carbon tetrachloride and dried to give 16.4 g of **4a**. Second crop (9.7 g) was obtained from the filtrate by refluxing for 8 hr, followed by standing overnight. Total yield of **4a** was 26.1 g (42.8%). Recrystallizations from ethanol afforded colorless needles, mp 244.5—245°.

Compounds (**4c** and **4d**) which were listed in Table II were prepared in a similar manner.

b) Borane Reduction of **2a**: The reduction was carried out as described for reduction of **2a** to **3a**. After treatment with conc. HCl, the reaction mixture was made basic with ammonia water, without isolation of the hydrochloride of **3a**, and extracted with dichloroethane. The organic layer was dried and evaporated. The residue was dissolved in carbon tetrachloride and the solution was refluxed for 8 hr. After cooling, the resultant precipitate was collected by filtration and dried to yield 5.10 g (57.3% from 10.2 g of **2a**) of **4a**, mp 238—241°.

Compound (**4b**) which was listed in Table II was prepared in a similar manner.

c) From the Hydrochloride of **3a**: To a suspension of the hydrochloride of **3a** in 50 ml of carbon tetrachloride was added 1.1 g of pyridine. The mixture was refluxed for 8 hr and allowed stand overnight at room temperature. Filtration and washing with water gave 3.0 g (83.4%) of **4a**, mp 232—238°.

5-Chloro-N-(2-hydroxyethyl)-3-phenylindole-2-carboxamide (10)——A mixture of 210 g of **1a** and 210 g of ethanolamine was heated with stirring at 145—156° until the calculated amount of alcohol had distilled off. After further stirring at 156—157° for 3 hr, 300 ml of toluene was added at the same rate as the distillate was collected. After about 3.2 liter of distillate was collected, the reaction mixture was cooled, and the resultant precipitate was collected by filtration, washed with water and dried to give 214 g (97.2%) of **10**, mp 180—187°. Recrystallizations from benzene gave colorless prisms, mp 188°. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 3410, 3390 (CONH), 3280 (OH), 3240 (indole NH), 1643 (CO), and 1552. *Anal.* Calcd. for $C_{17}H_{15}O_2N_2Cl$: C, 64.87; H, 4.80; N, 8.90; Cl, 11.26. Found: C, 64.65; H, 4.70; N, 8.49; Cl, 11.25.

5-Chloro-N-(2-chloroethyl)-3-phenylindole-2-carboxamide (11)——To a suspension of 29.3 g of **10** in 200 ml of toluene was added with stirring 17 g of thionyl chloride at room temperature. After further stirring at 30—34° for 1.5 hr, the reaction mixture was cooled and diluted with 70 ml of water. The precipitate was collected by filtration, washed thoroughly with water and dried to give 30.3 g (88.1%) of **11**, mp 195—199°. Recrystallizations from benzene afforded colorless needles, mp 198—199°. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 3400 (CONH), 3240 (indole NH), 1648 (CO), 1548, and 1527. Mass Spectrum *m/e*: 332 (28%, M$^+$), 295 (100), 253 (75), 251 (14), 238 (6), 224 (10), 219 (10), 216 (12), 203 (8), 199 (14), 190 (75) and 163 (21). *Anal.* Calcd. for $C_{17}H_{14}ON_2Cl_2$: C, 61.27; H, 4.24; N, 8.41; Cl, 21.28. Found: C, 61.19; H, 4.31; N, 8.21; Cl, 21.08.

Conversion of 11 to 4a and 5-Chloro-2-oxazolinyl-3-phenylindole (12)——To a solution of 28 g of **11** in 200 ml of DMF was added 33.6 g of potassium carbonate at 25—26° over a period of 30 min and the mixture was stirred at 50—64° for 1 hr. The cooled reaction mixture was poured into 600 ml of water, and the resultant precipitate was collected by filtration, washed with water and dried to give 24.5 g solid product. A small part (2.0 g), dissolved in a small volume of chloroform, was placed on a column of 70 g of silica gel. The column was eluted with ethyl acetate and fractions of 30 ml were collected. Evaporation of the fractions 4 and 5 gave 0.65 g (31.9% from **11**) of **12**, mp 184—186°. Two recrystallizations from benzene afforded white crystals, mp 185—186°. *Anal.* Calcd. for $C_{17}H_{13}ON_2Cl$: C, 68.80; H, 4.41; N, 9.44; Cl, 11.95. Found: C, 68.80; H, 4.43; N, 9.27; Cl, 11.95.

The fractions 9—22 were also combined and evaporated to give 0.90 g (44.2%) of **4a**, mp 236—240°, which was identical with the sample obtained from **2a** by mixture melting point and comparison of IR spectra.

The crude mixture (20 g) was suspended in 400 ml of carbon tetrachloride, and the suspension was stirred under reflux for 2 hr and allowed to cool to room temperature. After 2 hr, the crystal was collected by filtration and washed twice with 10 ml of carbon tetrachloride. The dried solid was pure **4a** by TLC: mp 236—238°; yield, 8.0 g (39.3%).

Conversion of 11 to 12 with 20% aq. NaOH in Ethanol——To a solution of 0.95 g of **11** in 30 ml of ethanol was added a mixture of 0.6 ml of 20% aq. NaOH and 0.6 ml of ethanol at 75°. After 5 min, the solvent was evaporated, and the residue was washed with water and filtered to yield 0.82 g (96.9%) of **12**, mp 177—181°, which was identical with the sample obtained above by comparison of TLC and IR.

Treatment of 12 with 3N HCl——A mixture of 0.20 g of **12** and 6 ml of 3N HCl was heated at 80° for 10 min. After evaporation of the solvent, the residue was recrystallized from EtOH to give 0.17 g (75.7%) of **11**, mp 198—200°, which was identical with the sample prepared from **10** by comparison of IR and TLC.

1-(5-Chloro-3-phenylindol-2-ylcarbonyl)aziridine (14)——To a stirred mixture of 0.8 g of aziridine, 30 ml of 2.3% aq. NaOH and 30 ml of benzene was added portionwise 4.7 g of 5-chloro-3-phenylindole-2-carboxylic acid chloride[3c] below 5° over a period of 20 min. After further stirring for 1 hr at 5°, the precipitate was collected by filtration and dried to give 2.80 g of **14**, mp 206—206.5°. The filtrates were separated, and the organic layer was washed with water, dried and evaporated to give an additional 1.76 g of **14**. Total yield was 4.56 g (94.9%). Recrystallizations from benzene afforded colorless pillars, mp 206—207°. *Anal.* Calcd. for $C_{17}H_{13}ON_2Cl$: C, 68.80; H, 4.41; N, 9.44; Cl, 11.95. Found: C, 68.88; H, 4.56; N, 9.23; Cl, 11.85.

Isomerization of 14——A solution of 0.60 g of **14** and 1.0 g of NaI in 75 ml of acetone was stirred at room temperature for 3 hr. The solvent was evaporated and the residue was partitioned between water and chloroform. The organic layer was separated, washed with water, dried and concentrated to a small volume, which was applied to a column of 50 g of silica gel. Fractions of 20 ml were collected. Elution with ethyl acetate gave 0.37 g (61.7%) of **12**, mp 182—184.5° in the fractions 5—9 and 0.22 g (36.7%) of **4a**, mp 240.5—242° in the fractions 12—22.

Treatment of 14 with 3N HCl——In a similar manner as described for 3N HCl treatment of **12**, **14** afforded 0.18 g (80.2% from 0.20 g of **14**) of **11**, mp 198—199°.

1-(2-Benzoyl-4-chlorophenyl)-2,3-piperazinedione (5a)——a) From **4a**: To a stirred suspension of 8.0 g of **4a** in 80 g of acetic acid was added portionwise a solution of 8.0 g of chromium trioxide in 8 ml of water. After stirring at 17—24° for 16 hr, the reaction mixture was poured into 500 ml of water and extracted with dichloroethane (three 100 ml portions). The organic layer was washed with 70 ml of 5% aq. NaOH, and filtered through a bed of Celite. The filtrates were separated, and the organic layer was washed with sat. aq. NaCl, dried and evaporated. The residue was stirred with 100 ml of toluene at 90° for 1 hr. The mixture was allowed to stand overnight at room temperature. Filtration and washing with toluene give 7.3 g (82.3%) of **5a**, mp 193—197°. An analytical sample was obtained after recrystallizations from aq. ethanol as colorless needles, mp 198—198.5°. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 3245 (NH), 1709, 1674 and 1660 (sh). Mass Spectrum *m/e*: 328 (23%, M^+), 258 (24), 244 (33), 223 (53), 180 (25), 166 (31), 105 (77) and 77 (100).

Compound (**5b**) which was listed in Table VI was prepared in a similar manner.

b) From the Hydrochloride of **3a**: To a suspension of 60 g of **3a** in 300 ml of acetic acid was added a solution of 60 g of chromium trioxide in 45 ml of water. The mixture was stirred at 18—22° for 3 hr. The reaction mixture was worked up as described in a) to give 39.2 g (75.4%) of **5a**, mp 197—198°, which was identical with the sample obtained in a) by mixture melting point and IR spectra comparison.

1-[4-Bromo-2-(2-pyridylcarbonyl)phenyl]-2,3-piperazinedione (5d)——A solution of 6.8 g of **4d** in 150 ml of acetic acid was ozonized with a stream of ozone-oxygen at 18°. The reaction mixture was diluted with water, made basic with ammonia water and extracted with chloroform. The chloroform extracts were washed with water, dried and evaporated. The residue was recrystallized from ethanol–benzene (1: 1) to give 1.3 g of starting material. Evaporation of the filtrate, followed by recrystallization from benzene, afforded 2.0 g (26.9%) of **5d**, mp 123—125° (decomp.).

Compound (**5c**) which was listed in Table VI was prepared in a similar manner.

7-Chloro-2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepine (6a)——To a suspension of 10 g of **5a** in 48 ml of methanol was added 105 ml of 8.2% aq. KOH. The mixture was stirred under reflux for 16 hr. After evaporation of methanol at atmospheric pressure, the mixture was cooled. The precipitate was collected by filtration, washed with water followed by cold methanol and dried to give 7.0 g (89.7%) of **6a**, mp 168—170°. Recrystallizations from ethanol afforded yellow plates, mp 173—173.5°. This material was identical with an authentic sample[7] by mixture melting point and comparison of IR spectra. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 3270 (NH) and 1610 (C=N). NMR ($CDCl_3$) δ: 3.70—4.02 (5H, m, 1H, D_2O exchangeable, $-CH_2CH_2NH-$) and 6.52—7.60 (8H, m, aromatic H).

Under similar conditions, but with NaOH as base, **6a** was obtained in 87.8% yield.

Compounds (**6b**, **6c**, and **6d**) which were listed in Table VII were prepared, using NaOH as base, in a similar manner.

[2-(2-Benzoyl-4-chloroanilino)ethyl]oxamic Acid (7a)——To a suspension of 3.3 g of **5a** in 50 ml of ethanol was added 5 ml of 20% aq. NaOH. The resultant solution was refluxed for 50 min. After evaporation of ethanol, the reaction mixture was diluted with 100 ml of water and acidified with conc. HCl. Filtration and washing with water gave 2.65 g (76.1%) of **7a**, mp 178—182° (decomp.). An analytical sample was obtained after recrystallizations from ethanol as yellow prisms, mp 191° (decomp.). IR $\nu_{\mathrm{max}}^{\mathrm{Nujol}}$ cm^{-1}: 3362 and 3337 (NH), 3170 (broad), 1743 and 1716 (COCOOH), 1624 ($C_6H_5C=O$), 1559, and 1513. NMR (DMSO-d_6) δ: 3.45 (4H, broad s, -CH_2CH_2-), 6.92—7.36 (3H, m, indole ring H), 7.53 (5H, s, C_6H_5), 8.35 (1H, broad s, D_2O exchangeable, NH) and 8.95 (1H, broad s, D_2O exchangeable, NH). Mass Spectrum *m/e*: 346 (weak, M^+), 302 (5%), 283 (12), 257 (14), 244 (60), 228 (12), 209 (7), 193 (20), 166 (32), ···, 44 (100). *Anal.* Calcd. for $C_{17}H_{15}O_4N_2Cl$: C, 58.88; H, 4.36; N, 8.08; Cl, 10.22. Found: C, 58.80; H, 4.11; N, 7.60; Cl, 10.06.

N-[2-(2-Benzoyl-4-chloroanilino)ethyl]formamide (8a)——A mixture of 1.0 g of **7a** and 20 ml of tetralin was heated with stirring at 194—195° for 30 min. After cooling, 300 ml of hexane was added and the mixture was allowed stand overnight in a refrigerator. The precipitate was collected by filtration and recrystallized from benzene to give 0.40 g (45.8%) of **8a** as yellow needles, mp 138—139°. Further recrystallization raised the melting point to 139—140°. IR $\nu_{\mathrm{max}}^{\mathrm{Nujol}}$ cm^{-1}: 3317, 3217, 3030, 1660 (CHO), 1633 ($C_6H_5C=O$), 1576, and 1516. Mass Spectrum *m/e*: 302 (11%, M^+), 284 (6), 257 (20), 244 (100), 228 (5), 209 (12) and 166 (50). *Anal.* Calcd. for $C_{16}H_{15}O_2N_2Cl$: C, 63.47; H, 4.99; N, 9.25; Cl, 11.71. Found: C, 63.51; H, 4.72; N, 8.95; Cl, 11.50.

7-Chloro-2,3-dihydro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepine (9)——To a stirred suspension of 10 g of **6a** in a mixture of 120 ml of toluene and 10 ml of THF was added a mixture of 21 g of a 16.6% ether-benzene solution of phenyllithium[13] and 20 ml of toluene at 0—5°. After 30 min, 8.3 g of methyl iodide in 10 ml of toluene was added below 5°, and the mixture was stirred at 5—10° for 4 hr and diluted with 100 ml of water. The organic layer was separated, washed with water and extracted with 5% aq. H_2SO_4 (three 50 ml portions). The aq. H_2SO_4 layer was made basic with 5% aq. NaOH and extracted with 200 ml of toluene. The toluene extract was washed successively with water, 5% aq. $NaHSO_3$ and sat. aq. NaCl, dried and evaporated. Recrystallization of the residue from hexane gave 7.9 g (75.0%) of **9** as almost colorless prisms, mp 102—103°. A comparison of **9** with an authentic sample prepared as described in the literature[10] showed the two compounds to be identical, IR $\nu_{\mathrm{max}}^{\mathrm{Nujol}}$ cm^{-1}: 1615 (C=N). NMR (CCl_4) δ: 2.72 (3H, s, CH_3), 3.33—3.78 (4H, m, -CH_2CH_2-) and 6.72—7.65 (8H, m, aromatic H). *Anal.* Calcd. for $C_{16}H_{15}N_2Cl$: C, 70.98; H, 5.58; N, 10.35; Cl, 13.09. Found: C, 71.17; H, 5.63; N, 10.35; Cl, 13.08.

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[13] Purchased from Foote Mineral Company.