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Benzodiazepines. IV.[1] A New Synthesis of 1-Diethylaminoethyl-substituted 1,4-Benzodiazepin-2-ones

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A new synthesis of 1-(2-diethylaminoethyl)-substituted 1,4-benzodiazepin-2-ones by ring enlargement of the corresponding 2-aminomethylindole derivatives is reported. A number of related compounds leading to these compounds were synthesized. Attempted chlorination of 5-chloro-1-(2-diethylaminoethyl)-3-(*o*-fluorophenyl)indole-2-carboxylic acid (VI) with thionyl chloride yielded 8-chloro-3,4-dihydro-2-ethyl-10-(*o*-fluorophenyl)-pyrazino [1,2-*a*] indol-1(2H)-one (VII). Chlorination of 5-chloro-3-phenylindole-2-carboxylic acid derivative (VIII) with thionyl chloride gave two products, the expected acid chloride (XVI) and the dimer (XVII).

In the previous publications,[1,3] it was reported that the 1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one derivatives were synthesized by ring enlargement of the 2-aminomethyl-3-phenylindole derivatives on treatment with chromic acid. As an extension of this work, we have applied this method to the synthesis of benzodiazepin-2-ones bearing diethylaminoethyl group in position 1. These compounds have been previously synthesized by condensation of N-unsubstituted benzodiazepin-2-ones with diethylaminoethyl chloride.[4]

The ethyl 5-chloro-3-phenylindole-2-carboxylate derivatives (IV) were prepared by the Fisher cyclization of the azo-esters (II) or hydrazones (III), which were made by the Japp–Klingemann reaction.

The Japp–Klingemann reaction is thought to proceed *via* the formation of the intermediate azo-ester which cleaves to give hydrazone.[5] Recently a few of reports on isolation of intermediate azo compounds have been published.[6] In this study, the azo-ester IIa has been obtained by coupling of *p*-chlorobenzenediazonium chloride with α-(*o*-fluorobenzyl)acetoacetate (Ia)under neutral or slightly acidic conditions. The same treatment of *p*-chlorobenzenediazonium chloride with α-benzylacetoacetate (Ic) also gave the corresponding azo-ester IIc. These compounds IIa and IIc were relatively stable and could be recrystallized from ethanol. The structure of these compounds was established from the elemental analysis and the infrared (IR), ultraviolet (UV) and nuclear magnetic resonance (NMR) spectra. The IR spectrum of IIa showed two carbonyl peaks at 1748 and 1713 cm^{-1} and no NH group. The UV spectrum of IIa exhibited a single maximum at 288 $m\mu$ (ε 14000). The NMR spectrum revealed the ethyl protons of the carboethoxy group as triplet and quartet at 8.77 τ and 5.75 τ, the methyl protons of the acetyl group as singlet at 7.81 τ and the methylene protons of the benzyl group as singlet at 6.33 τ. The azo-ester IIc showed similar spectra.

IIa and IIc were converted into the hydrazones IIIa and IIIc by treatment with ethanolic potassium hydroxide. The structure of III was confirmed by spectral comparison with the azo-

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[1] Part III: S. Inaba, T. Hirohashi and H. Yamamoto, *Chem. Pharm. Bull.* (Tokyo), **17**, 1263 (1969).

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

[3] H. Yamamoto, S. Inaba, T. Hirohashi and K. Ishizumi, *Chem. Ber.*, **101**, 4245 (1968).

[4] L.H. Sternbach, G.A. Archer, J.V. Earley, R.I. Fryer, E. Reeder and N. Wasyliw, *J. Med. Chem.*, **8**, 815 (1965).

[5] R.R. Philips, "Organic Reactions," Vol. 10, John Wiley and Sons, Inc., New York, N.Y., 1959, Chapter 2.

[6] *a*) H.C. Yao and P. Resnick, *J. Amer. Chem. Soc.*, **84**, 3514 (1962); *b*) B. Eistert and M. Regitz, *Ann.*, **666**, 97 (1963); *idem, Chem. Ber.*, **96**, 2290, 2304, 3120 (1963).

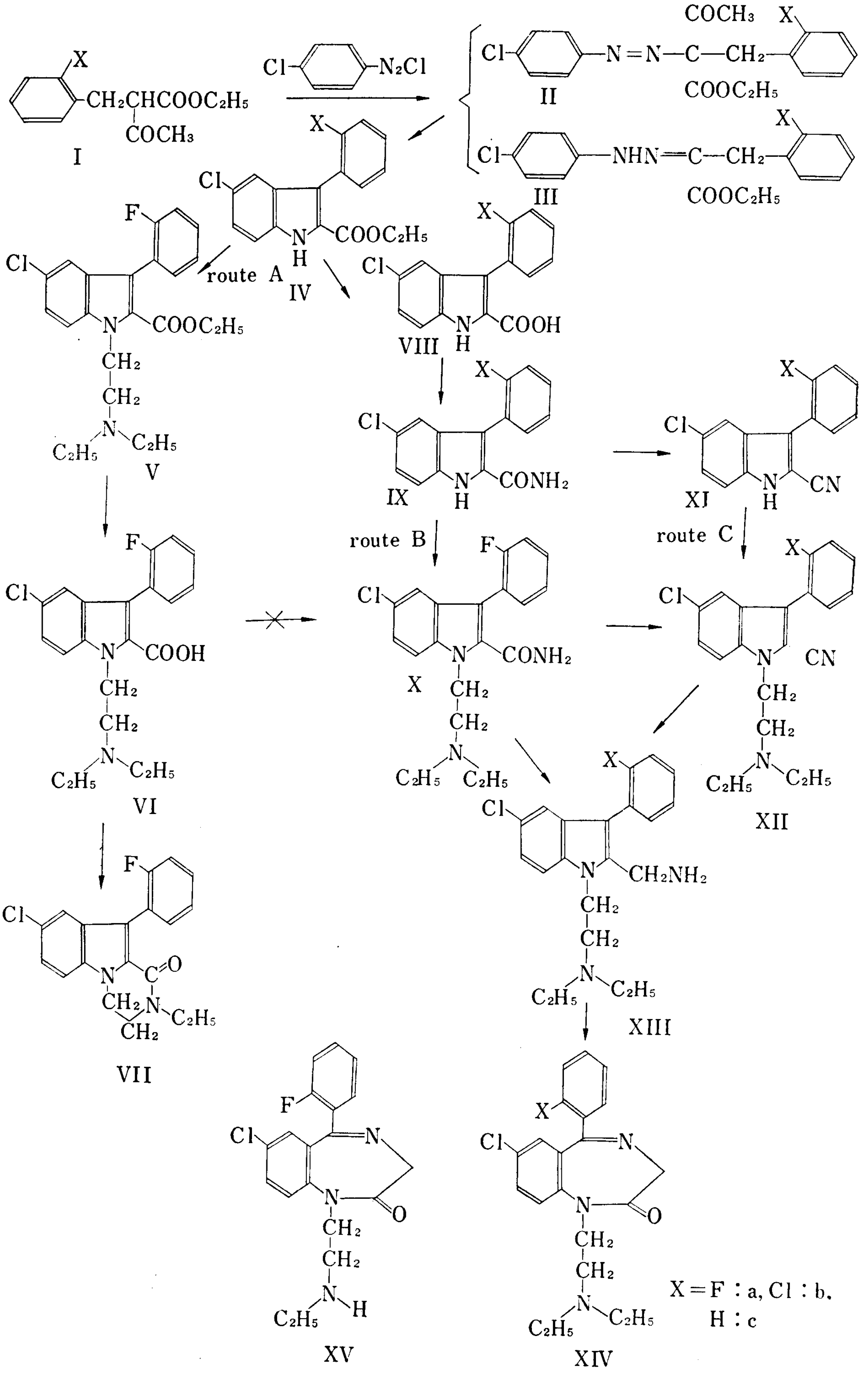
I
II
III
IV
V
VI
VII
VIII
IX
X
XI
XII
XIII
XIV
XV
route A
route B
route C
X=F : a, Cl : b,
H : c

Chart 1

ester II. The UV spectrum of IIIa showed maxima at 300 mμ (ε 16200) and 328 mμ (ε 24200). The IR spectra of IIIa and IIIc showed the NH peak and the carbonyl bands at 1712 and 1691—1693 cm^{-1}. In the NMR spectra, the signal, ascribable to the acetyl group, has disappeared and the NH signal was shown at 1.5—1.8 τ.

The Japp–Klingemann reaction of *p*-chlorobenzenediazonium chloride with ethyl α-(*o*-chlorobenzyl)acetoacetate (Ib) yielded the hydrazone (IIIb). The azo-ester (IIb) appeared to be unstable and cleave into the hydrazone IIIb. The structure of IIIb was assigned by the IR spectrum, which exhibited a single carbonyl band at 1698 cm^{-1} and the NH band at 3270 cm^{-1}. Treatment of the azo-ester II or the hydrazone III with hot ethanolic hydrogen chloride gave the corresponding indole esters IV. Alkylation of the indole ester IVa with sodium hydride and diethylaminoethyl chloride and subsequent hydrolysis gave the carboxylic acid VI. In an attempt to obtain the 5-chloro-1-(2-diethylaminoethyl)-3-(*o*-fluorophenyl)-indole-2-carboxamide (X) *via* acid chloride from VI, VI was treated with excess thionyl chloride. We obtained the intramolecular cyclization product VII instead of the expected acid chloride.

The structure of VII was indicated by the NMR spectrum, which revealed a three-proton triplet and a two-proton quartet for the ethyl group at 8.84 τ and 6.44 τ ($J=7$ cps), two two-proton signal at 6.34 τ and 5.82 τ for the other methylen groups and seven aromatic protons. The IR spectrum which exhibited a single carbonyl band at 1648 cm^{-1} and the mass spectrum with the parent ion at *m/e* 342 were compatible with the structure assigned.

When the 5-chloro-3-phenylindole-2-carboxylic acid derivative (VIII) prepared by hydrolysis of the ester IV was refluxed with 4 mole equivalents of thionyl chloride for 2 hours, it afforded the acid chloride (XVI) and the insoluble dimer (XVII).

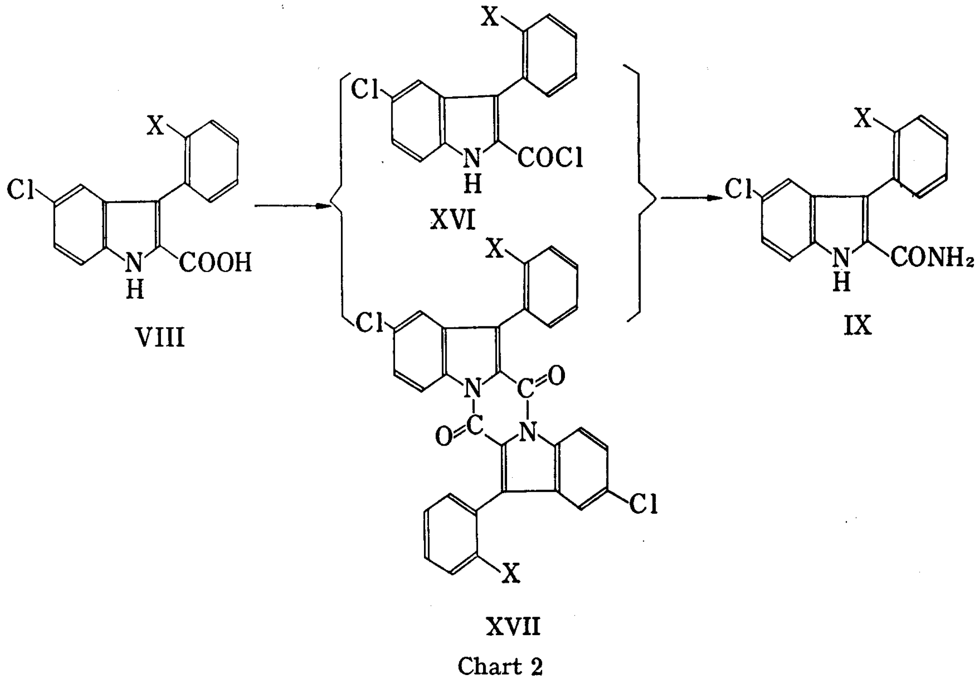

Chart 2

The dimer XVIIa could also be prepared by heating the acid chloride XVIa.

Borsche and Klein⁷⁾ reported that the similar compounds of this type were obtained from 3-phenylindole-2-carboxylic acid chlorides. We confirmed the structure of XVII by the IR and mass spectra. Table I, II and III show the properties of XVI and XVII.

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7) W. Borsche and A. Klein, *Ann.*, **548**, 64 (1941).

Table I. 5-Chloro-3-phenylindole-2-carboxylic Acid Chlorides XVI and Dimers XVII

Compd. No.	X	mp (°C)	Appearance ( ): Recryst. solvent	Yield (%)	IR ν_{max}^{Nujol} cm^{-1} NH	IR ν_{max}^{Nujol} cm^{-1} CO	NMR ($(CD_3)_2CO$)δ: NH
XVIa	F	160—162	prisms (ligroin)	97	3350	1720	11.45
XVIIb	F	>300	needles (DMF)	1		1709, 1697	
XVIa	Cl	142—144	prisms (ligroin)	77	3340	1714	11.60
XVIIb	Cl	>300	prisms (DMF)	8		1708	
XVIc	H	174—176	needles (ether)	50	3332	1707	11.38
XVIIc	H	>300	needles (DMF)	26		1695	

Compd. No.	Formula	Analysis (%) Calcd. C	H	N	Cl	Found C	H	N	Cl
XVIa	$C_{15}H_8ONCl_2F$	58.46	2.61	4.55	23.01	58.15	2.57	4.48	22.71
XVIIa	$C_{30}H_{14}O_2N_2Cl_2F_2$	66.30	2.60	5.16	13.05	65.91	2.53	5.16	12.92
XVIb	$C_{15}H_8ONCl_3$	55.50	2.48	4.31	32.77	55.54	2.43	4.30	32.14
XVIIb	$C_{30}H_{14}O_2N_2Cl_4$	62.53	2.45	4.86	24.61	62.89	2.39	4.90	24.94
XVIc	$C_{15}H_9ONCl_2$	62.09	3.13	4.83	24.44	62.06	3.12	4.74	24.08
XVIIc	$C_{30}H_{16}O_2N_2Cl_2$	71.02	3.18	5.52	13.98	71.30	3.18	5.33	13.92

Table II. Principal Peaks Present in the Mass Spectra of Acid Chlorides XVI and Dimers XVII

	XVIa *m/e* (%)[a]	XVIIa *m/e* (%)	XVIb *m/e* (%)	XVIIb *m/e* (%)	XVIc *m/e* (%)	XVIIc *m/e* (%)
M_D[b]		542 (91)		574 (3.3)		506 (77)
M_D–19		523 (19)				
M_D–35				539 (100)		
M_C[c]	307 (22)		323 (32)		289 (24)	
M_C–35			288 (70)		254 (36)	
M_C–36	271 (91)	271 (38)	287 (100)		253 (92)	253 (28)
M_C–70			253 (60)			
M_C–71			252 (47)	252 (33)		
M_C–99	208 (100)	208 (100)	224 (89)	224 (43)	190 (100)	190 (100)
M_C–125	182 (21)	182 (6)	198 (21)		164 (17)	164 (6.5)
M_C–126	181 (30)	181 (9)	197 (11)		163 (24)	163 (10)
M_C–135			188 (41)	188 (17)		
M_C–160			163 (42)			

[a] ( ): % of base peak
[b] M_D: the molecular ion of dimer XVII
[c] M_C: the molecular ion of acid chloride XVI

Table III. Isotope Abundances in the Mass Spectra of Acid Chlorides XVI and Dimers XVII

	XVIa (2Cl) % of M (*m/e* 307) Calcd.	Found	XVIIa (2Cl) % of M (*m/e* 542) Calcd.	Found	XVIb (3Cl) % of M (*m/e* 323) Calcd.	Found	XVIIb (4Cl) % of M (*m/e* 574) Calcd.	Found	XVIc (2Cl) % of M (*m/e* 289) Calcd.	Found	XVIIc (2Cl) % of M (*m/e* 506) Calcd.	Found
M	100	100	100	100	100	100	100	100	100	100	100	100
M+2	65.3	67	65.3	69	99.8	99	131.0	132	65.3	63	65.3	72
M+4	10.6	12	10.6	15	31.9	34	63.9	64	10.6	11	10.6	15

The IR spectra of XVI showed a carbonyl band at 1707—1720 cm^{-1} and a NH band at 3330—3350 cm^{-1}, whereas XVII showed a carbonyl band, shifting to lower frequencies than that of XVI and lacked an absorption ascribable to a NH group. The mass spectrum of XVIIc showed the parent ion (M^+) at *m/e* 506 and the relative ratio of M, M+2 and M+4 of XVIc and XVIIc closely resembled that calculated for a dichloro compound.8) The spectra of XVIc and XVIIc resembled each other in the region below *m/e* 253. The most intense peak in each spectrum was displayed at *m/e* 190. The *o*-F substituted compounds XVIa and XVIIa had fragmentation patterns very similar to those of the *o*-unsubstituted compounds XVIc and XVIIc, whereas the *o*-Cl substituted compounds XVIb and XVIIb showed the base peaks at *m/e* 287 (M_C-36) and *m/e* 539 (M_D-35). The M, M+2 and M+4 pattern indicated the presence of three chlorine atoms in XVIb and four in XVIIb. The above data established the structure of XVII as 2,9-dichloro-7,14-diphenyl-pyrazino[1,2-*a*, 4,5-*a'*]-diindole-6,13-dione.

The mixture of XVI and XVII prepared from the acid VIII was converted, without separation of both compounds, into the 5-chloro-3-phenylindole-2-carboxamide derivative (IX) by treatment with ammonia. Dehydration of the amide IX with phosphorous oxychloride gave a high yield of the 5-chloro-3-phenylindole-2-carbonitrile derivative (XI). N-Alkylation of the amide IX or the nitrile XI was carried out in the same manner as that used for the ester IV to yield the amide X and the 5-chloro-1-(2-diethylaminoethyl)-3-phenylindole-2-carbonitrile derivative (XII). The nitrile XIIa was also prepared by dehydration of the amide X. Both the amide X and the nitrile XII were reduced with lithium aluminum hydride to yield the 2-aminomethyl-5-chloro-1-(2-diethylaminoethyl)-3-phenylindole derivative (XIII).

Formation of XIIIa from the amide IXa by route C gave over-all yield of 81% but only a 49% yield by route B; therefore route C was preferable.

Oxidation of the aminomethylindole XIIIa with chromium trioxide in acetic acid resulted in the formation of the expected 7-chloro-1-(2-diethylaminoethyl)-1,3-dihydro-5-(*o*-fluorophenyl)-2H-1,4-benzodiazepin-2-one (XIVa). The IR and UV spectra of XIVa was identical with those of an authentic sample prepared from the reaction of 7-chloro-1,3-dihydro-5-(*o*-fluorophenyl)-2H-1,4-benzodiazepin-2-one9) with diethylaminoethyl chloride. This structure was further confirmed by mass spectral comparison with the published spectrum.10*a*) The NMR spectrum revealed methylen protons of the benzodiazepin-2-one ring as an AB system at 6.32 τ and 5.26 τ (J=10.5 cps). This magnetic nonequivalence of methylen protons appears to be characteristic of the benzodiazepin-2-one having a substituent in position 1.11) The two ethyl groups of the diethylaminoethyl side chain appeared as triplet and quartet at 9.09 τ and 7.54 τ (J=7 cps) and the other two methylen protons as triplet and multiplet at 7.49 τ (J=7 cps) and 6.55—5.70 τ.

The synthesis of XIVa by chromic acid-oxidation was, however, accompanied by the formation of a small amount of the N-desethyl analog10*b*) (XV) of XIVa. The structure of XV was assigned by spectral comparison with XIVa. The IR spectrum closely resembled that of XIVa. Although the NMR spectrum of XV was also similar to that of XIVa, integration indicated only 5 protons for the N-ethyl group of XV and an exchangeable proton ascribable to a NH group appeared as singlet at 8.12 τ. These facts revealed that one ethyl group on the side chain nitrogen atom of XIVa was replaced by a hydrogen atom.

Further study of oxidation of XIIIa showed that ozonolysis also caused the ring enlargement and the formation of XIVa in good yield. In this reaction the formation of the

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8) J.H. Beynon, "Mass Spectrometry and Its Application to Organic Chemistry," Elsevier, Amsterdam, 1960, p. 298.

9) Prepared by the method described in ref. 4.

10) *a*) M.A. Schwartz, F.M. Vane and E. Postma, *J. Med. Chem.*, 11, 770 (1968); *b*) J.V. Earley, R.I. Fryer, D. Winter and L.H. Sternbach, *ibid.*, 11, 774 (1968).

11) P. Nuhn and W. Bley, *Pharmazie*, 22, 532 (1967); W. Bley, P. Nuhn and G. Benndorf, *Arch. Pharm.*, 301, 444 (1968).

des-ethyl analog XV was not observed. XIVb and XIVc were also prepared by ozonolysis of XIIIb and XIIIc.

The ozonolysis was carried out by passing an ozone-oxygen or ozone-air stream in formic acid or acetic acid until about 1 mole equivalent of ozone was absorbed.

Thus, the synthesis of the benzodiazepin-2-one bearing diethylaminoethyl group in position 1 by ring enlargement of the corresponding 2-aminomethyl indole derivative has been accomplished and ozone has been revealed to be an effective oxidant.

The central nervous system effects of compound XIVa, XIVb and XIVc had been reported by Sternbach, *et al.*[4] Animal tests with these compounds in our laboratory showed XIVa to have potent anticonvulsant activity (antipentylenetetrazole activity) in mice, and potent taming effects against fighting mice, septal rat and aggressive monkey. Compounds XIVb and XIVc was much less potent than XIVa.

The general profile of tests showed Compound XIVa to be more potent than chlorodiazepoxide and less potent than diazepam.

Experimental

All melting points are uncorrected. IR spectra were measured on a Perkin Elmer 125 spectrophotometer; UV spectra on a Shimadzu SV-50-AL spectrophotometer, and NMR spectra on a Varian A-60-D instrument at 60 Mc and given in the τ scale with reference to tetramethylsilane as the 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-6E instrument with the direct sample inlet system; ionizing potential at 70 eV. Solvents used for extraction were dried over anhydrous Na_2SO_4 after extraction, and removed under reduced pressure.

Ethyl *α*-(*o*-Fluorobenzyl)acetoacetate (Ia)——The ester Ia was obtained from *o*-fluorobenzylchloride and ethyl acetoacetate by the method of Takizawa[12] in 76% yield. bp 159—161° (19 mmHg). IR ν_{max}^{cap} cm^{-1}: 1735 ($COCH_3$), 1715 ($COOC_2H_5$). *Anal.* Calcd. for $C_{13}H_{15}O_3F$: C, 65.55; H, 6.30. Found: C, 65.40; H, 6.04.

Ethyl *α*-(*o*-Chlorobenzyl)acetoacetate (Ib)——The ester Ib was obtained from *o*-chlorobenzylchloride and ethyl acetoacetate by the method of Clark and Johnson[13] in 72% yield. bp 130—140° (0.35 mmHg). IR ν_{max}^{cap} cm^{-1}: 1740 ($COCH_3$), 1725 ($COOC_2H_5$). *Anal.* Calcd. for $C_{13}H_{15}O_3Cl$: Cl, 13.92. Found: Cl, 13.54.

Ethyl *α*-(*p*-Chlorophenylazo)-*α*-(*o*-fluorobenzyl)acetoacetate (IIa)——A *p*-chlorobenzenediazonium chloride solution was made from *p*-chloroaniline (26.3 g, 0.21 mole), conc. HCl (69 g, 0.77 mole), H_2O (50 ml) and $NaNO_2$ (14.6 g, 0.21 mole), and the solution was partially neutralized with crystalline NaOAc (27.2 g, 0.20 mole). This solution was kept at 0°; while a solution of the ester Ia (47.6 g, 0.20 mole) in MeOH (200 ml) was reacted at 15° with KOAc (33.7 g, 0.34 mole) and then cooled to 0°. The diazo-solution was then added dropwise with stirring below 3°. After further stirring for 2 hr under cooling, the resultant precipitate was collected, washed with H_2O and dried to yield 68.3 g (90.7%) of orange prisms, mp 74—79°. Recrystallizations from EtOH afforded yellow pillars, mp 79—80°. IR ν_{max}^{Nujol} cm^{-1}: 1750 ($COCH_3$), 1715 ($COOC_2H_5$). UV λ_{max}^{MeOH} mμ (ε): 288 (13900). NMR ($CDCl_3$) τ: 8.77 (3H, t, J=7 cps, $CH_2C\underline{H}_3$), 7.81 (3H, s, $COCH_3$), 6.33 (2H, s, $C\underline{H}_2Ph$), 5.75 (2H, q, J=7 cps, $C\underline{H}_2CH_3$), 3.10—2.25 (8H, m, aromatic protons). *Anal.* Calcd. for $C_{19}H_{18}O_3N_2ClF$: C, 61.54; H, 4.86; N, 7.56; Cl, 9.58. Found: C, 61.20; H, 4.53; N, 7.31; Cl, 9.56.

Ethyl *α*-Benzyl-*α*(*p*-chlorophenylazo)acetoacetate (IIc)——*p*-Chloroaniline (131 g, 1.03 mole) was diazotized and coupled with ethyl *α*-benzylacetoacetate (220 g, 1.0 mole) as above to yield the azo-ester IIc (343 g, 96%), mp 54.5—61°. Recrystallizations from EtOH gave yellow prisms, mp 61—62.5°. IR ν_{max}^{Nujol} cm^{-1}: 1755 ($COCH_3$), 1717 ($COOC_2H_5$). NMR ($CDCl_3$) τ: 8.83 (3H, t, J=7 cps, $CH_2C\underline{H}_3$), 7.87 (3H, s, $COCH_3$), 6.4 (2H, s, $C\underline{H}_2Ph$), 5.79 (2H, q, J=7 cps, $C\underline{H}_2CH_3$), 2.90—2.20 (9H, m, aromatic protons). *Anal.* Calcd. for $C_{19}H_{19}O_3N_2Cl$: C, 63.71; H, 5.62; N, 7.81; Cl, 9.88. Found: C, 64.09; H, 5.24; N, 7.79; Cl, 9.88.

Ethyl *o*-Fluorophenylpyruvate *p*-Chlorophenylhydrazone (IIIa)——To a suspension of the azo-ester IIa (7.54 g) in EtOH (50 ml) was added 40% aq. KOH (3 ml) at 25—30° for 5 min. The reaction mixture were filtered off, washed thoroughly with H_2O and dried to give 5.4 g (80.6%) of crystals. Two recrystallizations from iso-PrOH gave orange prisms, mp 89—90°. IR ν_{max}^{Nujol} cm^{-1}: 3295, 3265 (NH), 1712, 1691 (CO). UV λ_{max}^{MeOH} mμ (ε): 328 (24200), 300 (16200). NMR ($CDCl_3$) τ: 8.65 (3H, t, J=7 cps, $C\underline{H}_2CH_3$) 6.05 (2H, s, $C\underline{H}_2Ph$), 5.67 (2H, q, J=7 cps, $C\underline{H}_2CH_3$), 2.95—2.67 (8H, m, aromatic protons), 1.65 and 1.53 (1H, NH). *Anal.* Calcd. for $C_{17}H_{16}O_2N_2ClF$: C, 60.99; H, 4.82; N, 8.37; Cl, 10.59. Found: C, 61.09; H, 4.91; N, 8.39; Cl, 10.41.

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[12] S. Takizawa, *Science Repts. Research Insts. Tohoku Univ.*, **4**, 311 (1952) [*C.A.*, **48**, 1958i (1954)].

[13] C.M. Clark and J.D.A. Johnson, *J. Chem. Soc.*, **1962**, 126.

Ethyl Phenylpyruvate *p*-Chlorophenylhydrazone (IIIc)——The hydrazone IIIc was obtained from IIc as above in 83% yield and recrystallized from EtOH gave yellow prisms, mp 91.5—94°. IR ν_{max}^{Nujol} cm^{-1}: 3230 (NH), 1712, 1693 (CO). NMR (CCl_4) τ: 8.73 (3H, t, $J=7$ cps, $CH_2\underline{CH_3}$), 6.20 (2H, s, $\underline{CH_2}Ph$), 5.84 (2H, q, $J=7$ cps, $\underline{CH_2}CH_3$), 3.03—2.80 (9H, m, aromatic protons), 1.77 (1H, s, NH). *Anal.* Calcd. for $C_{17}H_{17}O_2N_2Cl$: C, 64.46; H, 5.40; N, 8.84; Cl, 11.20. Found: C, 65.02; H, 5.47; N, 8.77; Cl, 11.16.

Ethyl *o*-Chlorophenylpyruvate *p*-Chlorophenylhydrazone (IIIb)——*p*-Chloroaniline (47.1 g, 0.368 mole) was diazotized and coupled with the ester Ib (93.6 g, 0.368 mole). An orange oil formed was extracted with ether. The ether layer was washed with H_2O, dried and evaporated. The residue, which contained a little amount of AcOH, was further washed with H_2O and dried to give 78.8 g (61.2%) of slightly yellow crystals, mp 123—125°. It was identified by its IR spectrum as the hydrazone IIIb. IR ν_{max}^{Nujol} cm^{-1}: 3270 (NH), 1698 ($COOC_2H_5$).

Ethyl 5-Chloro-3-(*o*-fluorophenyl)indole-2-carboxylate (IVa)——Dry HCl was passed into a stirred solution of the azo-ester IIa (126.4 g) in EtOH (250 ml) until NH_4Cl precipitated. The mixture was stirred at 60° for 2 hr and then cooled to 0°. The resultant precipitate was collected, washed with H_2O and dried to yield 86.9 g (72.5%) of colorless crystals, mp 188—189°. Recrystallizations from EtOH afforded colorless pillars, mp 188—189°. IR ν_{max}^{Nujol} cm^{-1}: 3310 (ind. NH), 1687 ($COOC_2H_5$). *Anal.* Calcd. for $C_{17}H_{13}O_2NClF$: C, 64.25; H, 4.09; N, 4.41; Cl, 11.18. Found: C, 64.28; H, 3.92; N, 4.04; Cl, 11.32.

Ethyl 5-Chloro-3-(*o*-chlorophenyl)indole-2-carboxylate (IVb)——The hydrazone IIIb was cyclized as above to IVb in 93.4% yield. Recrystallizations from EtOH gave colorless small prisms, mp 196—196.5°. IR ν_{max}^{Nujol} cm^{-1}: 3307 (ind. NH), 1677 ($COOC_2H_5$). *Anal.* Calcd. for $C_{17}H_{13}O_2NCl_2$: C, 61.10; H, 3.92; N, 4.19; Cl, 21.22. Found: C, 61.14; H, 3.98; N, 4.00; Cl, 20.91.

Ethyl 5-Chloro-3-phenylindole-2-carboxylate (IVc)——The ester IVc was obtained from the azo-ester IIc in 91% yield and recrystallized from EtOH to yield colorless needles, mp 178°—180°. It was identical with the authentical sample[3] through admixture and spectral comparison.

Ethyl 5-Chloro-1-(2-diethylaminoethyl)-3-(*o*-fluorophenyl)indole-2-carboxylate (V)——To a stirred solution of the ester IVa (47.7 g) in dimethylformamide (500 ml) and toluene (500 ml) was added 61% NaH oil dispersion (8 g). The mixture was stirred at room temperature for 1 hr and then at 40—50° for 1 hr. To this solution was added diethylaminoethyl chloride and the mixture was refluxed for 18 hr. The reaction mixture was poured into ice-water, the layers were separated and the aqueous layer was extracted with ether (three 300 ml portions). The organic layers were combined and washed with H_2O and dried. Evaporation of solvent furnished a pale yellow oil (66.9 g). Recrystallizations of the picrate from EtOH gave yellow small pillars, mp 138—139°. IR ν_{max}^{Nujol} cm^{-1}: 1709 ($COOC_2H_5$), 1568, 1319 (NO_2). *Anal.* Calcd. for $C_{29}H_{29}O_9N_5ClF$: C, 53.91; H, 4.50; N, 10.84; Cl, 5.50. Found: C, 53.87; H, 4.35; N, 10.65; Cl, 5.59.

5-Chloro-1-(2-diethylaminoethyl)-3-(*o*-fluorophenyl)-2-carboxylic Acid Hydrochloride (VI)——A solution of the ester V (50 g) in EtOH (500 ml) was refluxed with 85% KOH (13.8 g) for 2 hr. The residue on evaporation was dissolved in H_2O (300 ml), acidified with conc. HCl (70 ml) under cooling and extracted with $CHCl_3$ (400 ml). The extract was washed with H_2O, dried and evaporated to give a slightly yellow solid. Washing with ether afforded 42 g (81%) of crystalline powders, mp 225—226°. Recrystallizations from tetrahydrofuran gave colorless small prisms, mp 228—230°. IR ν_{max}^{Nujol} cm^{-1}: 1700 (COOH). *Anal.* Calcd. for $C_{21}H_{24}O_2N_3Cl_2F$: C, 59.30; H, 5.45; N, 6.59; Cl, 16.68. Found: C, 59.71; H, 5.47; N, 6.57; Cl, 16.55.

8-Chloro-3,4-dihydro-2-ethyl-10-(*o*-fluorophenyl)-pyrazino [1,2-*a*]indole-1(2H)-one (VII)——A mixture of the hydrochloride VI (2.13 g) and $SOCl_2$ (2.4 g) was refluxed for 3 hr. After excess $SOCl_2$ was evaporated, the residue was chromatographed on silica gel (70 g). Elution with $CHCl_3$ gave 0.84 g (49%) of a crystalline product, mp 185—186°. Recrystallization from benzene-petroleum benzin (1:1) gave colorless small prisms, mp 185—186°. IR ν_{max}^{Nujol} cm^{-1}: 1648 (CON$<$). NMR ($CDCl_3$) τ: 8.84 (3H, t, $J=7$ cps, $CH_2\underline{CH_3}$), 6.44 (2H, q, $J=7$ cps, $\underline{CH_2}CH_3$), 6.34 (2H, m, $CH_2\underline{CH_2}N(C_2H_5)CO$), 5.82 (2H, m, $\underline{CH_2}CH_2N(C_2H_5)CO$), 2.85—2.50 (7H, m, aromatic protons). Mass Spectrum *m/e*: 342 (M^+), 314, 222 (base peak), 208. *Anal.* Calcd. for $C_{19}H_{16}ON_2ClF$: C, 66.57; H, 4.70; N, 8.17; Cl, 10.35. Found: C, 66.43; H, 4.76; N, 7.98; Cl, 10.08.

5-Chloro-3-(*o*-fluorophenyl)indole-2-carboxylic Acid (VIIIa)——A solution of the ester IVa (4.8 g) in EtOH (60 ml) was refluxed with 85% KOH (1.8 g) for 2 hr. After evaporation of the solvent, the residue was dissolved in H_2O (50 ml) and acidified with conc. HCl (2 ml) under cooling. The resulting white precipitate was filtered off, washed thoroughly with H_2O and dried to give 4.35 g (100%) of colorless small needles, mp 250—252°. Recrystallizations from benzene raised the melting point to 254—255°. IR ν_{max}^{Nujol} cm^{-1}: 3465 (ind NH), 1685 (COOH). *Anal. Calcd.* for $C_{15}H_9O_2NClF$: C, 62.19; H, 3.13; N, 4.84; Cl, 12.24. Found: C, 62.43; H, 3.02; N, 4.80; Cl, 12.00.

5-Chloro-3-(*o*-chlorophenyl)indole-2-carboxylic Acid (VIIIb)——The ester IVb was hydrolysed as above in 90.3% yield. Recrystallizations from benzene afforded a colorless small prisms, mp 215.5—216°. IR ν_{max}^{Nujol} cm^{-1}: 3417 (ind. NH), 1670 (COOH). *Anal.* Calcd. for $C_{15}H_9O_2NCl_2$: C, 58.85; H, 2.96; N, 4.58; Cl, 23.16. Found: C, 59.19; H, 2.82; N, 4.64; Cl, 23.20.

5-Chloro-3-(*o*-chlorophenyl)indole-2-carboxylic Acid Chloride (XVIb) and 2,9-Dichloro-7,14-bis(*o*-chlorophenyl)-pyrazino [1,2-*a*, 4,5-*a'*]diindole-6,13-dione (XVIIb)——A mixture of the carboxylic acid VIIIb (3.06 g, 0.01 mole) and $SOCl_2$ (4.8 g, 0.04 mole) was refluxed for 2 hr. The excess $SOCl_2$ was removed *in vacuo* and the residue was dissolved in dry ether (20 ml). The yellow insoluble material was separated by filtration and washed thoroughly with ether to give 0.23 g (8%) of the dimer XVIIb. Recrystallizations from dimethylformamide afforded pale yellow small prisms, mp >300°. The ether filtrates were combined and evaporated. The residue was washed with petroleum ether to afford the acid chloride XVIb (2.5 g, 77%), mp 135—139°. Two recrystallizations from ligroin gave almost colorless prisms, mp 142—144°.

Other acid chlorides XVI and dimers XVII which were listed in Table I were prepared in a similar manner.

2,9-Dichloro-7,14-bis(*o*-fluorophenyl)-pyrazino [1,2-*a*, 4,5-*a'*]diindole-6,13-dione (XVIIa). From the Acid Chloride XVIIa——The acid chloride XVIa (0.3 g) was fused in an oil bath at 220° for 10 min. The resulting solid was washed with dry benzene to yield 0.17 g (64.3%) of the dimer XVIIa. Recrystallizations from dimethylformamide afforded pale yellow small needles, mp >300°, identical with the sample prepared from VIIIa in a similar manner as described for chlorination of VIIIb.

5-Chloro-3-(*o*-fluorophenyl)indole-2-carboxamide (IXa)——A mixture of XVIa and XVIIa prepared from VIIIa (30 g) was dissolved in ether (600 ml) without separation of both compounds and to this solution, the excess dry NH_3 gas was passed over a period of 1 hr under cooling and stirring. After further stirring for 1 hr at room temperature, the reaction mixture was cooled in an ice bath several hours. The resultant precipitate was collected, washed thoroughly with H_2O and dried to give the amide IXa (19.7 g), mp 213—214°. A second crop (7.3 g) was obtained from the filtrate after concentration. Total yield of IXa was 27 g (90%). Recrystallizations from tetrahydrofuran–benzene (1:1) gave colorless small needles, mp 227—228°. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 3477 (ind. NH), 3300, 3256, 3210 ($CONH_2$), 1658 ($CONH_2$). *Anal.* Calcd. for $C_{15}H_{10}ON_2ClF$: C, 62.40; H, 3.50; N, 9.70; Cl, 12.28. Found: C, 62.72; H, 3.48; N, 9.74; Cl, 12.30.

5-Chloro-3-(*o*-chlorophenyl)indole-2-carboxamide (IXb)——The amide IXb was obtained from VIIIb as above in 100% yield and crystallized from EtOH to give colorless small needles, mp 210—212°. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 3475 (ind. NH), 3300, 3260, 3210 ($CONH_2$), 1649 ($CONH_2$). *Anal.* Calcd. for $C_{15}H_{10}ON_2Cl_2$: C, 59.04; H, 3.30; N, 9.18; Cl, 23.24. Found: C, 59.34; H, 3.44; N, 9.33; Cl, 23.16.

5-Chloro-3-(*o*-fluorophenyl)indole-2-carbonitrile (XIa)——A mixture of the amide IXa (20.7 g) and $POCl_3$ (107 g) was refluxed for 20 min, HCl being copiously evolved. The cooled solution was poured over crushed ice (800 g) and made basic with 28% aq. NH_4OH (300 ml). The yellow solid was collected, washed thoroughly with H_2O and dried to give 18.7 g (98.7%) of the nitrile IXa, mp 185—186°. Recrystallizations from benzene afforded colorless needles, mp 187—188°. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 3330 (ind. NH), 2221 (CN). *Anal.* Calcd. for $C_{15}H_8N_2ClF$: C, 66.54; H, 2.96; N, 10.35; Cl, 13.12. Found: C, 66.80; H, 2.80; N, 10.51; Cl, 12.95.

5-Chloro-3-(*o*-chlorophenyl)indole-2-carbonitrile (XIb)——The nitrile XIb was prepared as above in 95.8% yield. For analysis a sample was recrystallized from benzene to give colorless small prisms, mp 167.5—168°. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 3318 (ind. NH), 2234 (CN). *Anal.* Calcd. for $C_{15}H_8N_2Cl_2$: C, 62.74; H, 2.81; N, 9.76; Cl, 24.69. Found: C, 62.92; H, 2.63; N, 9.55; Cl, 24.52.

5-Chloro-3-phenylindol-2-carbonitrile (XIc)——The nitrile XIc was recrystallized from EtOH to give colorless needles, mp 217—219°. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 3305 (ind. NH), 2225 (CN). *Anal.* Calcd. for $C_{15}H_9N_2Cl$: C, 71.30; H, 3.59; N, 11.09; Cl, 14.03. Found: C, 71.73; H, 3.73; N, 11.03; Cl, 14.00.

5-Chloro-1-(2-diethylaminoethyl)-3-(*o*-fluorophenyl)indole-2-carboxamide (X)——Under the same condition as described for alkylation of IVa but with 4 hr refluxing, the amide IXa gave a solid product, mp 120—123.5° in 78% yield. Recrystallizations from iso-PrOH afforded colorless small pillars, mp 126—128°. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 3170, 3050 (broad, $CONH_2$), 1665 ($CONH_2$). NMR ($CDCl_3$) τ: 9.10 (6H, t, $J=7.5$ cps, $2\times CH_2C\underline{H}_3$), 7.50 (4H, q, $J=7.5$ cps, $2\times C\underline{H}_2CH_3$), 7.13 (2H, t, $J=7$ cps, $Et_2NC\underline{H}_2CH_2$), 5.47 (2H, t, $J=7$ cps, $Et_2NCH_2C\underline{H}_2$), 3.60 (1H, broad, $CONH_2$), 2.90—2.40 (7H, m, aromatic protons). *Anal.* Calcd. for $C_{21}H_{23}ON_3ClF$: C, 65.03; H, 5.98; N, 10.83; Cl, 9.14. Found: C, 65.58; H, 6.07; N, 10.63; Cl, 9.12.

5-Chloro-1-(2-diethylaminoethyl)-3-(*o*-fluorophenyl)indole-2-carbonitrile (XIIa)——i) From the Nitrile XIa: The nitrile XIa was alkylated similarly to yield a yellow oil, which was solidfied with petroleum ether. The solid (94.5%), mp 57—58°, was recrystallized from petroleum ether to give colorless prisms, mp 59—61°. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 2230 (CN). NMR (CCl_4) τ: 9.12 (6H, t, $J=7$ cps, $2\times CH_2C\underline{H}_3$), 7.50 (4H, q, $J=7$ cps, $2\times C\underline{H}_2CH_3$), 7.23 (2H, t, $J=7$ cps, $Et_2NC\underline{H}_2CH_2$), 5.72 (2H, t, $J=7$ cps, $Et_2NCH_2C\underline{H}_2$), 3.00—2.30 (7H, m, aromatic protons). *Anal.* Calcd. for $C_{21}H_{21}N_3ClF$: C, 68.19; H, 5.72; N, 11.36; Cl, 9.59. Found: C, 68.06; H, 5.53; N, 11.07; Cl, 9.57.

ii) From the Amide Xa: A mixture of the amide Xa (10 g) and $POCl_2$ (7.9 g) in toluene (20 ml) was refluxed for 3 hr. The solution was cooled and diluted with H_2O (20 ml). The precipitate was collected by filtration, washed with H_2O and dried to give the hydrochloride of the nitrile XIIa (8.5 g), mp 155—170°. From the mother liquor another crop (1.5 g, mp 175—184°) was obtained, total yield: 10 g (95.4%). Three recrystallizations from iso-PrOH gave colorless needles, mp 191—192°. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 2222 (CN). *Anal.* Calcd. for $C_{21}H_{22}N_3Cl_2F$: C, 62.12; H, 5.46; N, 10.35; Cl, 17.47. Found: C, 62.11; H, 5.31; N, 10.25; Cl, 17.28.

The free base was obtained and recrystallized from petroleum ether to give colorless prisms, mp 59—61°. This was identical with the one obtained from X through admixture and IR spectra comparison.

5-Chloro-3-(*o*-chlorophenyl)-1-(2-diethylaminoethyl)indole-2-carbonitrile (XIIb)——The nitrile XIIb was prepared from XIb quantitatively in the form of a viscous oil. Recrystallizations of the hydrochloride from iso-PrOH gave colorless needles, mp 156—157°. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 2550, 2360 (broad, $-NH^+$), 2215 (CN).

Anal. Calcd. for $C_{21}H_{22}N_3Cl_3$: C, 59.65; H, 5.25; N, 9.94; Cl, 25.16. Found: C, 59.56; H, 5.38; N, 9.97; Cl, 25.11.

5-Chloro-1-(2-diethylaminoethyl)-3-phenylindole-2-carbonitrile (XIIc)——The nitrile XIIc was prepared from XIc in 88.9% yield. Recrystallizations from petroleum ether afforded colorless prisms, mp 70—70.5°. IR ν_{max}^{Nujol} cm^{-1}: 2220 (CN). *Anal.* Calcd. for $C_{21}H_{22}N_3Cl$: C, 71.68; H, 6.30; N, 11.94; Cl, 10.08. Found: C, 71.97; H, 6.42; N, 11.97; Cl, 10.11.

2-Aminomethyl-5-chloro-1-(2-diethylaminoethyl)-3-(*o*-fluorophenyl)indole Dihydrochloride (XIIIa)——i) From the Amide X: The amide X (267 g) was added to a stirred suspension of $LiAlH_4$ (79 g) in dry ether (5.01iter). Stirring was continued at reflux for 6 hr. After cooling and cautions addition of H_2O (500 ml), the ether layer was separated, dried and evaporated. The residue was dissolved in EtOH (100 ml) and to this solution was added 20% HCl–EtOH (400 ml). After cooling the resulting precipitate was filtered off and dried to give 195 g (63%) of crystalline product, mp 243—244° (decomp.). Repeated recrystallizations from EtOH afforded colorless needles, mp 254—255° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 2713—2320, 1990 ($-NH_3^+$, $-NH^+$). *Anal.* Calcd. for $C_{21}H_{27}N_3Cl_3F$: C, 56.45; H, 6.09; N, 9.40; Cl, 23.81. Found: C, 56.08; H, 6.04; N, 9.14; Cl, 24.33.

ii) From the Nitrile XIIa: A solution of the nitrile XIIa (19.8 g) in dry ether (30 ml) was added to a stirred suspension of $LiAlH_4$ (2.38 g) in dry ether (400 ml) below 25°. After refluxing for 4 hr, work-up as above gave 18.7 g of pale yellow crystals, mp 254—255° (decomp.). From the mother liquor another crop (0.7 g) was obtained, total yield: 19.4 g (86.8%). This compound was identical with the one obtained from X through admixture and spectral comparison.

2-Aminomethyl-5-chloro-3-(*o*-chlorophenyl)-1-(2-diethylaminoethyl)indole Dihydrochloride (XIIIb)——The reduction of the nitrile XIIb was carried out as described for reduction of XIIa. Recrystallizations from aq. EtOH afforded colorless crystals, mp 252—254° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 2710—2310 (broad, $-NH_3^+$, $-NH^+$). *Anal.* Calcd. for $C_{21}H_{27}N_3Cl_4$: C, 54.44; H, 5.87; N, 9.07; Cl, 30.61. Found: C, 53.96; H, 5.85; N, 8.76; Cl, 30.43.

2-Aminomethyl-5-chloro-1-(2-diethylaminoethyl)-3-phenylindole Dihydrochloride (XIIIc)——The dihydrochloride of XIIIc was obtained similarly from the nitrile XIIc in 91.4% yield and recrystallized from iso-PrOH to give colorless needles, mp 235—236° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 3410, 3325, 2710—2610, 2320 ($-NH_3^+$, $-NH^+$). *Anal.* Calcd. for $C_{21}H_{28}N_3Cl_3$: C, 58.81; H, 6.58; N, 9.80; Cl, 24.80. Found: C, 58.67; H, 6.54; N, 9.59; Cl, 25.04.

7-Chloro-1-(2-diethylaminoethyl)-1,3-dihydro-5-(*o*-fluorophenyl)-2H-1,4-benzodiazepin-2-one (XIVa)——i) CrO_3 Oxidation: To a suspension of the dihydrochloride of XIIIa (148 g) in AcOH (750 ml) was added dropwise with stirring a solution of CrO_3 (95.8 g) in H_2O (70 ml) at 25—30°. The mixture was stirred at room temperature for 22 hr and added dropwise to a stirred mixture of 28% aq. NH_4OH (900 ml), H_2O (1.6 l) and CH_2Cl_2 (1.5 l) at 10—20°. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (three 500 ml portions). The combined CH_2Cl_2 layer was washed with H_2O, dried and evaporated to leave an oil (165 g), which was chromatographed on silica gel (650 g). Elution with 3% EtOH–$CHCl_3$ gave an oil (63 g) which was treated with excess EtOH–HCl. After evaporation of the solvent, the residual oil was taken up in hot iso-PrOH (200 ml). The solution was cooled and the crystalline precipitate was collected by filtration, washed with iso-PrOH and dried to yield 41 g (27.9%) of the dihydrochloride of XIVa, mp 207—209° (decomp.). This compound was purified by dissolving it in EtOH, filtering the solution and crystallizing the residual oil, after removal of the solvent, from iso-PrOH. Repeated purifications afforded slightly yellow small prisms, mp 215.5—217.5° (decomp.) (reported[4]) mp 190—220°). IR ν_{max}^{Nujol} cm^{-1}: 2505—2350 ($-NH^+$), 1935, 1925 ($C=\overset{+}{\underset{|}{N}}-H$), 1680 (CON<). *Anal.* Calcd. for $C_{21}H_{25}ON_3Cl_3F$: C, 54.74; H, 5.47; N, 9.12; Cl, 23.08. Found: C, 54.82; H, 5.26; N, 8.93; Cl, 23.12.

Further elution of the column with 20% EtOH–$CHCl_3$ gave an oil (6.9 g). Rechromatography yielded 0.7 g (0.6%) of the monoethylamino derivative XV as a brown viscous oil. IR ν_{max}^{cap} cm^{-1}: 1676 (CON<). NMR (CCl_4) τ: 9.09 (3H, t, $J=7$ cps, $CH_2C\underline{H}_3$), 8.12 (1H, s, NH), 7.50 (2H, q, $J=7$ cps, $C\underline{H}_2CH_3$), 7.33 (2H, t, $J=7$ cps, $-CH_2C\underline{H}_2NHEt$), 6.33, 5.27 (2H, doublet-d, AB type, $J=10.5$ cps, $COCH_2$), 6.60—5.50 (2H, m, $-C\underline{H}_2CH_2NHEt$), 3.10—2.20 (7H, m, aromatic protons).

Recrystallization of the dihydrochloride from MeOH–ether gave prisms, mp 212° (decomp.) (reported[10b]) 215—217°). IR ν_{max}^{Nujol} cm^{-1}: 2700—2100, 1900 ($-NH_2^+$, $C=\overset{+}{\underset{|}{N}}-H$), 1687 (CON<). *Anal.* Calcd. for $C_{19}H_{21}ON_3Cl_3F$: C, 52.73; H, 4.89; N, 9.71; Cl, 24.58. Found: C, 52.35; H, 5.08; N, 9.44; Cl, 24.26.

ii) Ozonolysis: a) With Ozone-Oxygen in HCOOH: A solution of the dihydrochloride of XIIIa (250 g, 0.559 mole) in HCOOH (2.5 kg) was ozonized at 11—14° with an ozone-oxygen stream containing 0.86 mole of ozone /m^3. Excess ozone was delivered and titration of the iodide trap showed about 0.8 mole equivalent reacted. The solvent was evaporated at 50° (bath temperature), and the residual oil was dissolved in ice-water (1 liter), made basic with 28% aq. NH_4OH and extracted with toluene (three 1 liter portions). The combined organic layer was washed with H_2O, dried and evaporated. The residue was dissolved in iso-PrOH (200 ml) with warming and treated with 26.5% iso-PrOH–HCl (227 g) under cooling. After chilling in a refrigerator overnight, the precipitate was collected, washed with cold iso-PrOH and dried to give the dihydrochloride of XIVa (186.5 g, y, 72.0%), mp 209—210° (decomp.). This was identical with the one obtained in (i) through IR spectra comparison.

A solution of the salt in H_2O (1 liter) was made basic with 28% aq. NH_4OH and extracted with toluene (three 500 ml portions). The combined organic layer was washed with H_2O, dried and evaporated. The residual oil was crystallized and recrystallized from ligroin to give the pure base as colorless small pillars, mp 82—83°. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1672 (CON<). UV $\lambda_{\max}^{\text{MeOH}}$ mμ (ε): 228 (32000), 317 (2100). NMR (CCl_4) τ: 9.09 (6H, t, J=7 cps, 2×$CH_2C\underline{H}_3$), 7.54 (4H, q, J=7 cps, 2×$C\underline{H}_2CH_3$), 7.49 (2H, t, J=7 cps, $Et_2NC\underline{H}_2CH_2$), 6.32, 5.26 (2H, doublet-d, AB type, J=10.5 cps, $COCH_2$), 6.55—5.70 (2H, m, $Et_2NCH_2C\underline{H}_2$), 3.15—2.19 (7H, m, aromatic protons). Mass Spectrum *m/e*: 387 (M^+), 315, 273, 259, 245. *Anal.* Calcd. for $C_{21}H_{23}ON_3ClF$: C, 65.02; H, 5.98; N, 10.83; Cl, 9.14. Found: C, 65.08; H, 5.84; N, 10.66; Cl, 9.23.

b) With Ozone-Air in AcOH: A solution of the hydrochloride of XIIIa (100 g) in AcOH (1.0 kg) was ozonized with 1.5 mole equivalents of ozone in an air stream at 17—18.5°. Work-up as above afforded 64.8 g (62.8%) of the dihydrochloride of XIVa, mp 210.5—212° (decomp.).

iii) From 7-Chloro-1,3-dihydro-5-(*o*-fluorophenyl)-2H-1,4-benzodiazepin-2-one: XIVa was prepared from 7-chloro-1,3-dihydro-5-(*o*-fluorophenyl)-2H-1,4-benzodiazepin-2-one by the method of Sternbach, *et al.*[4)] Purification of the dihydrochloride from iso-PrOH gave pale yellow small prisms, mp 198—207° (decomp.). This was identical with the sample obtained from XIIIa through IR and UV spectra comparison.

7-Chloro-5-(*o*-chlorophenyl)-1-(2-diethylaminoethyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (XIVb)——A solution of the dihydrochloride XIIIb (6.0 g) in HCOOH (60 g) was treated with a stream of ozone-oxygen at 10—18°. The reaction mixture was diluted with H_2O (200 ml), made basic with 28% aq. NH_4OH and extracted with ether (three 50 ml portions). The residual oil (3.75 g) was chromatographed on silica gel (120 g). Elution with AcOEt gave an oil (1.65 g, 31.7%), which was crystallized and recrystallized from petroleum-ether to give colorless prisms, mp 66—67.5° (reported[4)] mp 68—70°). IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1683 (CON<). NMR (CCl_4) τ: 9.00 (6H, t, J=7 cps, 2×$CH_2C\underline{H}_3$), 7.43 (4H, q, J=7 cps, 2×$C\underline{H}_2CH_3$), 7.38 (2H, t, J=7 cps, $Et_2NC\underline{H}_2CH_2$), 6.30, 5.26 (2H, doublet-d, AB type, J=10 cps, $COCH_2$), 6.39—5.88 (2H, m, $Et_2NCH_2C\underline{H}_2$), 3.07 (1H, d, J=2.5 cps, C_6-H), 2.72—2.22 (6H, m, aromatic protons). *Anal.* Calcd. for $C_{21}H_{23}ON_3Cl_2$: C, 62.38; H, 5.73; N, 10.39; Cl, 17.54. Found: C, 62.24; H, 5.91; N, 10.39; Cl, 17.47.

7-Chloro-1-(2-diethylaminoethyl)-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (XIVc)——A solution of the dihydrochloride of XIIIc (8.56 g) in AcOH (86 g) was treated with a stream of ozone-oxygen at 17—20°. Work-up as above gave an oil (2.4 g, 32.5%) which was solidified with petroteum ether. Recrystallizations from petroleum-ether gave colorless prisms, mp 62—63°. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1688, 1670 (CON<). NMR ($CDCl_3$) τ: 9.18 (6H, t, J=7 cps, 2×$CH_2C\underline{H}_3$), 7.59 (4H, q, J=7 cps, 2×$C\underline{H}_2CH_3$), 7.42 (2H, t, J=7 cps, $Et_2NC\underline{H}_2CH_2$), 6.50—5.50 (2H, m, $Et_2NCH_2C\underline{H}_2$), 2.78—2.32 (8H, m, aromatic protons). *Anal.* Calcd. for $C_{21}H_{24}ON_3Cl$: C, 68.19; H, 6.54; N, 11.36; Cl, 9.59. Found: C, 68.03; H, 6.48; N, 11.34; Cl, 9.57.
The above sample was recrystallized from pentane to afford colorless pillars, mp 72—73° (reported[4)] mp 79 81°).

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