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Studies on Benzoheterocyclic Derivatives. XIII.[1] Synthesis and Pharmacological Actions of Indoline Derivatives. (4)

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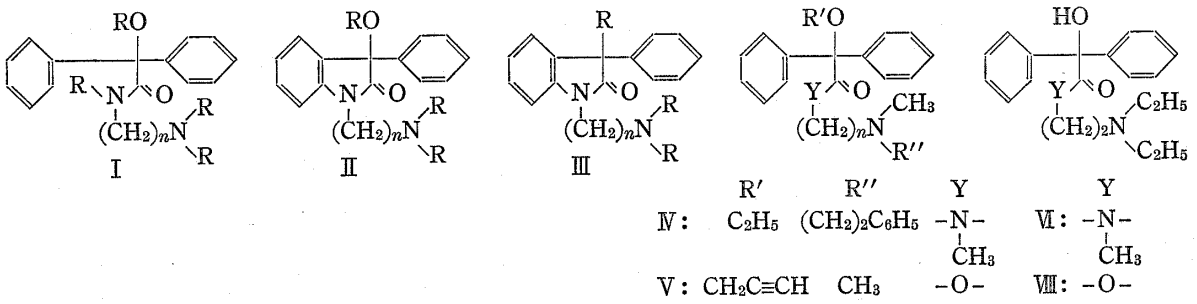
Thirty one derivatives of 3-alkoxy-1[ω-(N-substituted amino)-3-phenylindolin-2-one and related compounds were synthesized for pharmacological testing. As a preliminary screening test compounds were tested for analgetic-antiphlogistic activity by anti-writhing test in mice. Acute toxicity and gross behavioral changes in mice were also determined. The majority of the compounds produced anti-writhing activity.

A number of benzilamide derivatives have been observed to possess significant biological activities. It is interesting that the structure type (I) can be viewed as open versions of 3-alkoxy-1[ω-(N,N-dialkylamino)alkyl]-3-phenylindolin-2-one (II), therefore structure (II) which also has similar structural features may be expected to possess similar pharmacological activities with I.



	R′	R″	Y
IV:	C_2H_5	$(CH_2)_2C_6H_5$	$-N(CH_3)-$
V:	$CH_2C{\equiv}CH$	CH_3	$-O-$

	Y
VI:	$-N(CH_3)-$
VII:	$-O-$

Chart 1

From the facts that both IV[3] and V[4] have potent analgesic activity, and both VI[5] and VII[6] show anticholinergic action, it is possible to say ester function ($-\overset{O}{\overset{\|}{C}}-O-$) and amide function ($-\overset{O}{\overset{\|}{C}}-NR-$) are bioisosteric, and the replacement of the former with the latter probably brings about similar biological activities. In II homologues, it is possible to expect similar activities with biological activities which can be observed on V or VII.

In the preceeding article[1] we reported about the synthesis of 3-alky-1[ω-(N-substituted amino)alkyl]-3-phenylindolin-2-ones (III) and related compounds, and also described their inhibitory activity against acetic acid-induced writhing syndrome, prior to the investigation of antiphlogistic-analgesic activity against Carrageenin or Kaolin-induced edema. We also

1) Part XII: N. Hirose, S. Sohda, S. Kuriyama, and S. Toyoshima, *Chem. Pharm. Bull.* (Tokyo), **20**, 1669 (1972).
2) Location: *Koishikawa 4–6–10, Bunkyo-ku, Tokyo.*
3) J. Krapko and C.F. Turk, *J. Med. Chem.*, **6**, 547 (1963).
4) *a*) Rhein Chemie G. m. b. H., Belg. pat. 617668; *b*) D. Kupke and S. Geissler, *Arzneimittel-Forsch*, **13**, 312 (1963).
5) J. Krapko, U. S. pat., 2733256 (1956).
6) E.F. Blicke and C.E. Maxwell, *J. Am. Chem. Soc.*, **64**, 428 (1942).

reported that some of these derivatives possessed potent anti-writhing syndrome activity and that they concurrently possessed relatively high toxicity.

In order to investigate the influence resulting from the exchange alkyl group at position 3 for alkoxy group, 3-alkoxy-1[ω-(N-substituted amino)alkyl]-3-phenylindolin-2-ones (II) and the related compounds were synthesized, moreover their inhibitory action on writhing syndrome produced by acetic acid as the preliminary screening test for antiphlogistic-analgesic activity was examined. As it was possible to predict roughly the activities of substance on central or autonomic nervous system by investigation of the influence on general behavior,[7] observation of the gross behavioral changes was carried out.

Chemistry

The synthetic routes used to obtain these compounds are shown in Chart 2.

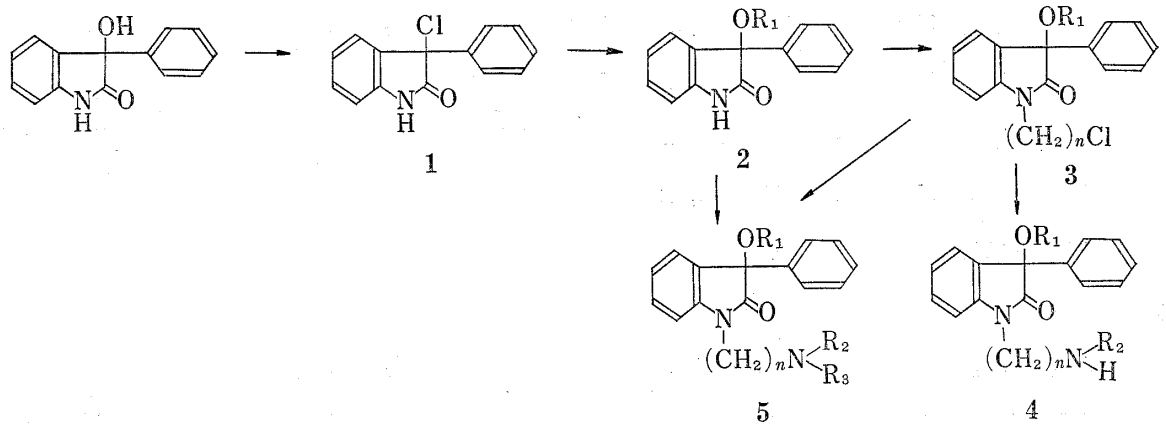
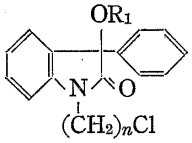


Chart 2

The starting material for these synthesis was 3-hydroxy-3-phenylindolin-2-one[8] which was easily obtainable by Grignard reaction of isatin with phenylmagnesium bromide. 3-Alkoxy-3-phenylindolin-2-ones (**2**) were prepared *via* 3-chloro-3-phenylindolin-2-one, *viz.*,

Table I. 3-Alkyl-1-(ω-chloroalkyl)-3-phenylindolin-2-ones (3)

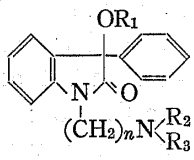


Compd. No.	R_1	n	bp (°C/mmHg) (mp °C)	Yield (%)	Formula	Appearance (Recrystn. solvent)	Analysis (%) Calcd. C	H	N	Found C	H	N
3a	CH_3	2	(110—112)	80.9	$C_{17}H_{16}O_2NCl$	scales (IPA)	67.65	5.35	4.64	67.50	5.22	4.65
3b	CH_3	3	(93— 95)	81.6	$C_{18}H_{18}O_2NCl$	needles (IPA)	68.45	5.76	4.44	68.24	5.70	4.51
3c	C_2H_5	2	(115—117)	83.9	$C_{18}H_{18}O_2NCl$	scales (IPA)	68.45	5.76	4.44	68.44	5.75	4.61
3d	C_2H_5	3	191—193/0.6	75.4	$C_{19}H_{20}O_2NCl$	viscous oil	69.18	6.12	4.25	69.00	6.29	4.27

7) S. Irwin, "Animal and Clinical Pharmacologic Techniques in Drug Evaluation," III, J.H. Nodine and P.E. Siegler, Ed., Year Book Publishers, Chicago, III, 1964, pp. 36—54

8) M. Kuhn, *Monatsh. Chem.*, **31**, 750 (1910).

TABLE II.[a] 3-Alkoxy-1-[ω-(N-substituted amino)alkyl]-3-phenylindolin-2-ones (4) and (5)



Compd. No.	R_1	R_2	R_3	n	bp(°C/mmHg) (mp °C)	Yield (%)	Formula (salt)	mp (°C)[b] appearance	Analysis (%) Calcd. / Found C	H	N
4a	CH_3	CH_3	H	2	209—210/0.5	68.5	$C_{18}H_{20}O_2N_2 \cdot HCl$	215—216 needles	64.94 (65.04)	6.37 (6.35)	8.42 (8.28)
4b	CH_3	C_2H_5	H	2	175—177/0.3	76.2	$C_{19}H_{22}O_2N_2 \cdot HCl$	190—192 needles	65.78 (65.82)	6.70 (6.80)	8.08 (8.25)
4c	CH_3	CH_3	H	3	195—198/1.0	75.4	$C_{19}H_{22}O_2N_2 \cdot HCl \cdot \frac{1}{2}H_2O$	198—200 needles	64.11 (64.57)	6.81 (6.51)	7.87 (7.77)
4d	CH_3	C_2H_5	H	3	205—206/1.2	65.4	$C_{20}H_{24}O_2N_2 \cdot HCl \cdot \frac{1}{2}H_2O$	211—212 needles	64.93 (65.56)	7.07 (6.81)	7.57 (7.45)
4e	C_2H_5	CH_3	H	2	188—190/0.4	69.3	$C_{19}H_{22}O_2N_2 \cdot HCl$	221—222 needles	65.78 (65.44)	6.70 (6.55)	8.08 (8.27)
4f	C_2H_5	C_2H_5	H	2	198—205/0.5	79.9	$C_{20}H_{24}O_2N_2 \cdot HCl \cdot \frac{1}{2}H_2O$	209—211 needles	64.93 (65.08)	6.96 (7.02)	7.57 (7.82)
4g	C_2H_5	C_2H_5	H	3	166—168/0.3	78.3	$C_{21}H_{26}O_2N_2 \cdot HCl$	204—206 needles	67.26 (67.02)	7.27 (7.07)	7.47 (7.31)
5a	CH_3	CH_3	CH_3	2	182—186/0.4	72.0	$C_{19}H_{23}O_2N_2 \cdot HCl \cdot \frac{1}{2}H_2O$	223(dec.) needles	64.12 (64.14)	6.81 (6.53)	7.87 (8.01)
5b	CH_3	C_2H_5	C_2H_5	2	202—205/0.6	70.1	$C_{21}H_{36}O_2N_2$ (M) $\cdot \frac{1}{2}H_2O$	106—108 needles	64.78 (64.79)	6.75 (6.36)	6.05 (5.95)
5c	CH_3	$(CH_2)_5$		2	205—207/0.4	65.7	$C_{22}H_{22}O_2N_2$ (M)	145—147 needles	66.93 (67.02)	6.49 (6.51)	6.01 (5.87)
5d	CH_3	$(CH_2)_2O(CH_2)_2$		2	(118—120)[c]	70.6	$C_{21}H_{24}O_3N_2$ (M) $\cdot \frac{1}{2}H_2O$	147—148 columns	62.87 (62.85)	6.13 (5.94)	5.87 (5.77)
5e	CH_3	CH_3	CH_3	3	177—178/0.3	73.8	$C_{20}H_{24}O_2N_2$ (F)	147—150 needles	65.43 (65.69)	6.42 (6.38)	6.36 (6.64)
5f	CH_3	C_2H_5	C_2H_5	3	197—200/0.4	70.8	$C_{22}H_{28}O_2N_2$ (F)	164—165 needles	66.64 (66.61)	6.90 (6.78)	5.98 (5.75)
5g	CH_3	$(CH_2)_5$		3	211—215/0.5	74.6	$C_{23}H_{28}O_2N_2$ (M)	117—119 needles	67.47 (67.24)	6.72 (6.57)	5.83 (5.63)
5h	CH_3	$(CH_2)_2O(CH_2)_2$		3	215—219/0.4	71.9	$C_{22}H_{26}O_3N_2$ (F) $\cdot \frac{1}{2}H_2O$	166—167 needles	63.52 (63.39)	6.37 (6.78)	5.70 (7.81)
5i	C_2H_5	CH_3	CH_3	2	170—175/0.2	69.4	$C_{20}H_{24}O_2N_2 \cdot HCl \cdot \frac{1}{2}H_2O$	213—214 needles	64.95 (65.39)	7.10 (6.78)	7.57 (7.81)
5j	C_2H_5	C_2H_5	C_2H_5	2	181—185/0.4	71.1	$C_{22}H_{28}O_2N_2$ (F) $\cdot \frac{1}{2}H_2O$	162—164 needles	65.38 (64.88)	6.98 (6.63)	5.87 (5.67)
5k	C_2H_5	$(CH_2)_5$		2	(92—94)[c]	80.5	$C_{23}H_{28}O_2N_2$ (F) $\cdot \frac{1}{2}H_2O$	191—193 needles	66.23 (66.54)	6.81 (6.62)	5.72 (5.78)
5l	C_2H_5	$(CH_2)_2O(CH_2)_2$		2	(122—124)[c]	78.6	$C_{22}H_{26}O_3N_2$ (M) $\cdot \frac{1}{2}H_2O$	174—175 needles	63.52 (63.22)	6.37 (5.91)	5.70 (5.38)
5m	C_2H_5	CH_3	CH_3	3	189—192/0.4	72.9	$C_{21}H_{26}O_2N_2$ (M)	198—200 prisms	66.05 (65.98)	6.67 (6.62)	6.16 (5.98)
5n	C_2H_5	C_2H_5	C_2H_5	3	185—189/0.4	76.3	$C_{23}H_{30}O_2N_2$ (F) $\cdot \frac{1}{2}H_2O$	182—184 columns	65.96 (66.10)	7.17 (7.08)	5.70 (5.84)
5o	C_2H_5	$(CH_2)_5$		3	220—224/0.6	68.3	$C_{24}H_{30}O_2N_2$ (F) $\cdot H_2O$	154—155 needles	65.60 (65.64)	7.09 (6.94)	5.47 (5.30)
5p	C_2H_5	$(CH_2)_2O(CH_2)_2$		3	232—237/0.6	65.6	$C_{23}H_{28}O_3N_2$ (M)	123—125 needles	65.30 (64.89)	6.51 (6.43)	5.64 (5.39)

a) On Table II and III, letters (M), (F) and (O) represent respectively maleic acid ($C_4H_4O_4$), fumalic acid ($C_4H_4O_4$) and Oxalic acid ($C_2H_2O_4$). The compounds listed in the formula column were used for microanalysis and pharmacological screening tests.
b) recrystd. from IPA
c) recrystd. from small amount of IPE

the material was chlorinated into **1** with thionyl chloride, and without purification (**1**) was converted into **2** by treating with appropriate alcohols using a modified Bruce's method.[9] 3-Alkoxy-1(ω-chloroalkyl)-3-phenylindolin-2-one (**3**) were prepared by the reaction with **2**, appropriate ω-chloroalkyl bromide and sodium amide. Reaction of **3** with excessive amount of monoalkyl amine produced 3-alkoxy-1[ω-(N-alkylamino)alkyl]-3-phenylindolin-2-ones (**4**), and with dialkyl amine afforded 3-alkoxy-1[ω-(N,N-dialkylamino)alkyl]-3-phenylindolin-2-ones (**5**) which were also prepared by the alkylation of **2** with correspoding ω-(N,N-dialkylamino)-alkyl chlorides in the presence of sodium amide. To prepare the compounds of structural type (**6**), 3-phenylindolin-2-one was treated with ω-(N,N-dialkylamino)alkyl chloride in the presence of sodium amide or sodium alcoholate, but the products were not **6** but 3[ω-(N,N-dialkylamino)alkyl]-derivatives.[10] Accordingly, reduction of **5** with sodium dihydro-bis(2-methoxyethoxy)aluminate (SDB) was carried out under the similar conditions as described for the reduction of 3-alkyl-1[ω-(N,N-dialkylamino)alkyl]-3-phenylindolin-2-ones,[1] and then 1[ω-(N,N-dialkylamino)alkyl]-3-phenylindolin-2-ones (**6**) resulted in place of the corresponding indoline or indole derivatives.

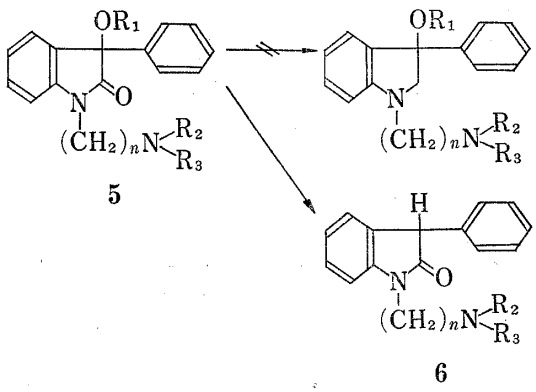
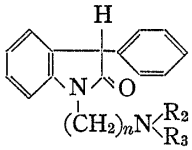


Chart 3

Table III. 1-[ω-(N,N-Dialkylamino)alkyl]-3-phenylindolin-2-ones (**6**)



Compd. No.	R_2	R_3	n	bp (°C/mmHg)	Yield (%)	Formula (salt)	mp (°C)[a] appearance	Analysis (%) Calcd. Found C	H	N
6a	CH_3	CH_3	2	182—184/0.6	80.6	$C_{18}H_{20}ON_2$ ·HCl	248—249 leaflets	68.22 (68.07)	6.69 (6.60)	8.84 (8.65)
6b	C_2H_5	C_2H_5	2	190—192/0.9	74.3	$C_{20}H_{24}ON_2$ (O)	164—167 needles	66.30 (66.38)	6.58 (6.47)	7.03 (7.38)
6c	$(CH_2)_5$		2	202—203/0.3	82.2	$C_{21}H_{24}ON_2$ ·HCl	224—226 needles	70.66 (70.39)	7.07 (7.30)	7.85 (7.80)
6d	$(CH_2)_2O(CH_2)_2$		2	220—222/0.9	75.5	$C_{20}H_{22}O_2N_2$ ·HCl	189—191 needles	66.92 (66.69)	6.47 (6.42)	7.80 (7.89)
6e	CH_3	CH_3	3	193—194/0.9	80.1	$C_{19}H_{22}ON_2$ (F)·H_2O	173—175 prisms	64.45 (64.27)	6.59 (6.23)	6.53 (6.51)
6f	C_2H_5	C_2H_5	3	195—197/0.5	82.4	$C_{21}H_{26}ON_2$ (M)	93— 95 needles	68.46 (68.58)	6.90 (6.95)	6.38 (6.52)
6g	$(CH_2)_5$		3	215—216/0.8	72.6	$C_{22}H_{26}ON_2$ ·HCl	216—217 needles	71.22 (71.21)	7.35 (7.42)	7.55 (7.36)
6h	$(CH_2)_2O(CH_2)_2$		3	230—231/0.9	69.5	$C_{21}H_{24}O_2N_2$ ·HCl	177—179 needles	67.63 (67.48)	6.77 (7.01)	7.51 (7.54)

a) recrystd. from IPA

9) J.M. Bruce and F.K. Sutcliffe, *J. Chem. Soc.*, **1957**, 4789.
10) G. Palazzo and V. Rosnat, *Gazz. Chim. Ital.*, **83**, 211 (1953).

As described in the previous paper[1] 3-alkyl-3-phenylindolin-2-ones and 3-alkyl-1[ω-(N,N-dialkylamino)alkyl]-3-phenylindolin-2-ones were reduced with SDB to afford 3-alkyl-3-phenylindolines and 3-alkyl-1[ω-(N,N-dialkylamino)alkyl]-3-phenylindolines. On the other hand, the reduction products of alkoxy derivatives (**5**) were not the indoline derivatives, but **6** as described above, which lost the alkoxy group at position 3 from **5**. It is interesting that as to 3-alkyl analogues (III) the reduction products were 3-alkyl-3-phenyl-1-substituted indolines resulting from conversion of >N–CO– to >N–CH_2–, while pertaining 3-alkoxy analogues, the products were not the indoline derivatives, but 3-phenyl-1-substituted indolin-2-ones resulting from the replacement of alkoxy group by hydrogen. Then, the reduction of 3-alkyl- (**7**) or 3-alkoxy-3-phenylindolin-2-ones (**2**) was carried out with SDB to investigate the general pattern of behavior of this reduction reagent for these compounds. The results are summarized in Table IV.

Table IV. Reduction of Some Indolin-2-one Derivs. with Sodium Dihydro-bis(2-methoxy-ethoxy)aluminate (SDB)

Amides (0.02 mole)	SDB (mole)	Reflux (hr)	Products (yield: %)
3-Methoxy-3-phenylindolin-2-one (**2e**)	0.02	2	3-phenylindole (**12**) (63%)
3-Ethoxy-3-phenylindolin-2-one (**2f**)	0.02	2	**12** (59%)
3-Hydroxy-3-phenylindolin-2-one (**2g**)	0.02	2	**12** (48%)
3-Methoxy-1-methyl-3-phenylindolin-2-one (**2h**)	0.06	2	2-hydroxy-3-methoxy-1-methyl-3-phenylindolin-2-one (**10h**) 72%)
	0.06	10	**10h** (57%)+1-methyl-3-phenylindolin-2-one (**11h**) (12%)
3-Methyl-3-phenylindolin-2-one (**7a**)	0.02	2	unreacted material+3-methyl-3-phenylindoline (**9a**) (41%)
	0.06	2	**9a** (88%)
3-Ethyl-3-phenylindolin-2-one (**7b**)	0.02	2	unreacted material+3-ethyl-3-phenylindoline (**9b**) (45%)
	0.06	2	**9b** (89%)
1,3-Dimethyl-3-phenylindolin-2-one (**7c**)	0.02	2	2-hydroxy-1,3-dimethyl-3-phenylindoline (**8c**) (75%)
	0.06	2	1,3-dimethyl-3-phenylindoline (**9c**) (72%)
1,3-Diethyl-3-phenylindolin-2-one (**7d**)	0.02	2	2-hydroxy-1,3-diethyl-3-phenylindoline (**8d**) (85%)
	0.06	2	1,3-diethyl-3-phenylindoline (**9d**) (84%)

It is suggested that SDB follows similar reduction mechanism as lithium aluminum hydride, the reduction reaction involves two routes (A and B) as to 3-alkyl analogues (**7**) and 3-alkoxy analogues (**2**) respectively, and then the reaction stops at various stages involved in the reduction of amide moiety to give various products as illustrated in Chart 4.

Reduction was carried out under the following condition; to a stirred solution of amide (**7** or **2**) in dry benzene was added dropwise a solution of SDB in dry benzene at ordinary temperature, and the mixture was refluxed to complete the reaction for 2 hours. As for 3-alkyl analogues (**7**) (route A), when 1,3-dialkyl-3-phenylindolin-2-ones (**7c, d**) were treated with large excess of SDB, the products were corresponding 1,3-dialkyl-3-phenylindolines (**9c, d**). The infrared (IR) spectrum showed the absence of carbonyl group and hydroxy group, and nuclear magnetic resonance (NMR) spectrum indicated the presence of methylene at position 2. As for the signals due to C_2-geminal protons, **9c** gave quartet (2H, AB system) centered at 3.28 ppm (J_{AB}=8 Hz, δ_{AB}=10 Hz), and **9d** gave singlet (2H) at 3.37 ppm. Further the mass spectra ofthese compounds supported the structure of **9c, d** for their fragmentation.

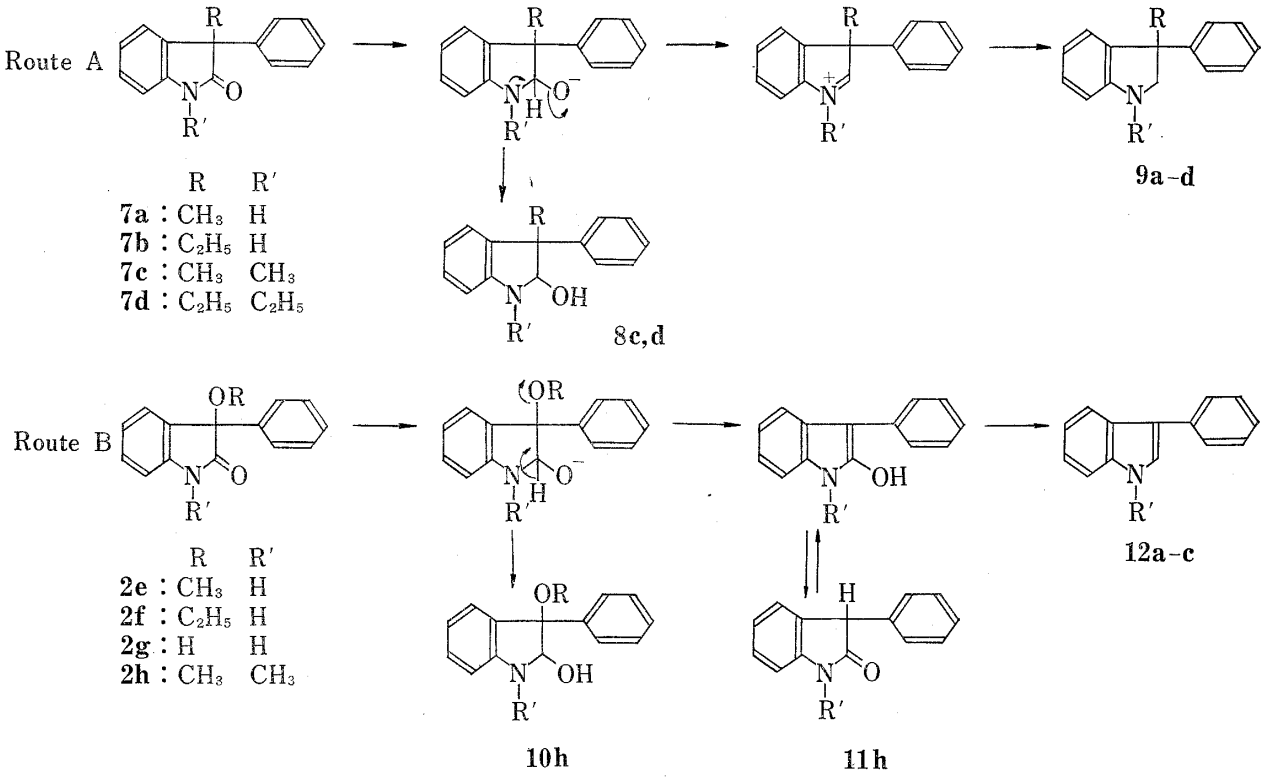


Chart 4

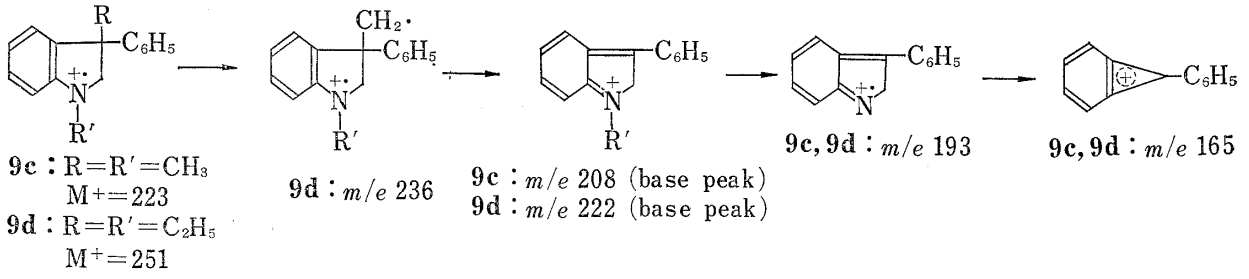


Chart 5

Being treated with equimolar of SDB, **7c,d** gave the corresponding carbinolamines (**8c,d**). **8c** was colorless prisms (mp 93—95°), and the IR spectrum showed the presence of hydroxy group (ν_{max}^{Nujol} cm^{-1}; 3300) but no carbonyl group. The mass spectrum gave the fragmentation which could support the structure of **8c** as illustrated in Chart 6 and Table V.

The NMR spectrum of **8c** in dimethyl-d_6-sulfoxide showed singlet (3H) due to C_3-methyl at 1.58 ppm, singlet (3H) due to N-methyl at 2.70 ppm, doublet (1H) due to C_2-proton centered at 4.79 ppm (J=7 Hz) and doublet (1H) due to hydroxy group centered at 5.95 ppm (J=7 Hz). When D_2O was added, the signal at 5.95 ppm disappeared and the signal at 4.79 ppm changed to a singlet. Meanwhile the determination of NMR spectrum of **8c** in deuterochloroform gave different results; it showed two singlets (3H) due to C_3-methyl at 1.59 and 1.71 ppm (the relative intensity ratio 1: 1), singlet (3H) due to N-methyl at 2.77 ppm, two slightly broad singlets due to C_2-proton at 4.60 and 4.80 ppm, and broad signal due to hydroxy group at 2.0 ppm. The spectrum of **8d** in deuterochloroform showed two overlapped triplets (3H) due to methyl of C_3-ethyl group centered at 0.82 and 0.88 ppm, two overlapped triplets (3H) due to methyl of N-ethyl group centered at 1.15 and 1.20 ppm, two overlapped quartets due to methylene of C_3-ethyl group centered at 2.10 and

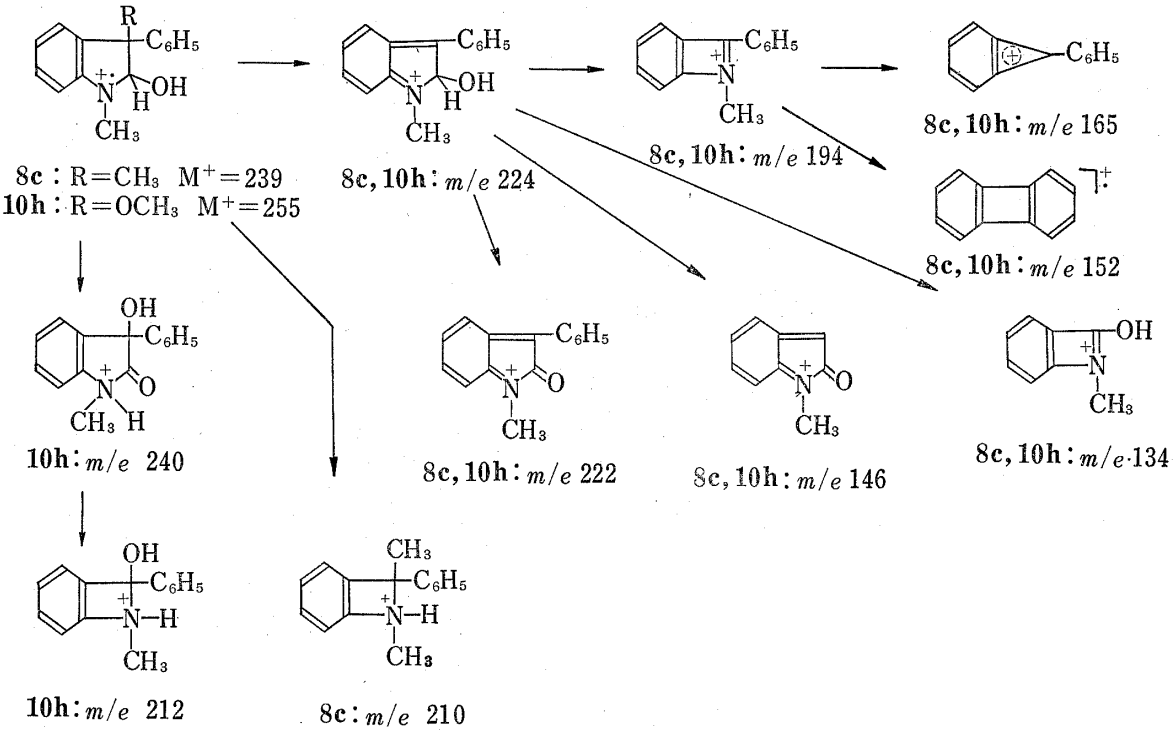


Chart 6

TABLE V. Exact Mass Measurements of **8c** and **10c**[a]

Compds.	*m/e*	Obsd.	Calcd.	Composition
8c	239[b]	0.1305	0.1310	$C_{16}H_{17}ON$
	224	0.1055	0.1075	$C_{15}H_{14}ON$
	222	0.0918	0.0918	$C_{15}H_{12}ON$
	210	0.1261	0.1280	$C_{15}H_{16}N$
	194	0.0957	0.0969	$C_{14}H_{12}N$
	165	0.0964	0.0704	$C_{13}H_9$
	152	0.0600	0.0625	$C_{12}H_8$
	146	0.0594	0.0605	C_9H_8ON
	134	0.0601	0.0605	C_8H_8ON
10h	255[b]	0.1267	0.1259	$C_{16}H_{17}O_2N$
	240	0.1022	0.1024	$C_{15}H_{14}O_2N$
	224	0.1060	0.1075	$C_{15}H_{14}ON$
	222	0.0917	0.0918	$C_{15}H_{12}ON$
	212	0.1057	0.1075	$C_{14}H_{14}ON$
	194	0.0967	0.0969	$C_{14}H_{12}N$
	165	0.0674	0.0704	$C_{13}H_9$
	152	0.0596	0.0625	$C_{12}H_8$
	146	0.0583	0.0605	C_9H_8ON
	134	0.0612	0.0605	C_8H_8ON

a) Mass values are based on $^{12}C=12.0000$. b) base peak

2.22 ppm, two overlapped quartets due to methylene of N-ethyl group centered at 3.38 and 3.48 ppm, and two broad singlets due to C_2-proton at 4.86 and 5.03 ppm. From these facts, it is supposed that the compounds (**8c,d**) are equiamount mixture of cis-trans isomers at position 2 and 3. Both **8c** and **8d** showed only one spot on thin-layer silica gel GF-$CHCl_3$ or silica gel GF-IPE. Then the following attempt was carried out; **8c** was reduced further with large excess of SDB under reflux, and afforded an amine, bp 136—140° (0.8 mmHg), which was identified with **9c** by means of IR and NMR spectrum.

The reduction of 3-alkyl-3-phenylindolin-2-ones (**7a,b**) with large excess of SDB afforded corresponding 3-alkyl-3-phenylindolines (**9a,b**).[1] However, the reduction of **9a,b** with equimolar of SDB did not give the expected 2-hydroxy analogues (**8a,b**), but the mixture of (**9a,b**) and the unreacted material. Regarding 3-alkoxy analogues (**2**) (route B), when 3-methoxy-1-methyl-3-phenylindolin-2-ones (**2h**) was treated with large excess of SDB, the product was 2-hydroxy-3-methoxy-3-phenylindoline (**10h**), and this formulation was confirmed by its NMR spectrum which showed singlet (3H) due to methoxy group at 3.20 ppm, singlet (3H) due to N-methyl at 2.81 ppm, singlet (1H) due to C_2-proton at 4.50 ppm and broad signal (1H) due to hydroxy group at 3.4 ppm. In this case, the spectrum of **10h**, unlike those of **8c,d**, did not indicate existence of the isomers, and **10h** gave only one spot on thin-layer sillica gel GF- $CHCl_3$. The mass fragmentation was consistent with the structure of **10h** (Chart 6 and Table V). Being refluxed for 10 hours under the same condition as described above, **2h** gave the mixture of **10h** and small amount of 1-methyl-3-phenylindolin-2-one[11] **11h** which were derived by the elimination of methanol from **10h**. The reduction of **5** to **6** described above seems to follow this mechanism. 3-Alkoxy-3-phenylindolin-2-ones (**2e—g**) were reduced to 3-phenylindole[12] (**12**) *via* (**11**). It is reported[13] that lithium aluminum hydride reduces 1-methylindolin-2-one to 1-methylindoline and 1-methylindole, but regarding to **7a,b** the products were mixture of unreacted material and 15—24% of **9a,b** in spite of treatment with excess molar of lithium aluminum hydride in tetrahydrofuran solution under reflux for 14 hours.

Table VI. Pharmacological Data of Anti-writhing Activity and Acute Toxicity

	Dose mg/kg (*i.p.*)	Compd. No. 4 a	b	c	d	e	f	g	5 a	b	c	d	e	f	g	h	i	j	k	l	m	n	o	p	6 a	b	c	d	e	f	g	h	APB P	B	Z[a-c]
Anti-writhing activity[d]	25	0	1	4	0	1	2	0	4	2	2	1	1	5	0	3	0	1	0	0	0	0	0	3	2	2	1	1	4	0	0	3	1	3	4
	50	1	2	3	0	0	2	1	3	3	3	3	4	4	1	4	4	0	0	1	1	2	3	2	3	2	3	0	2	2	0	0	2	3	5
	100	2	5	5	1	3	5	2																	5	5	1/1	2	5	5	0/1	3/3	5	3	5
Acute toxicity[e]	50	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0	4	0	0	0	4	2	0	0	0
	200	2	4	5	5	5	4	5	0	0	0	0	0	0	4	2	3	2	2	0	4	5	3	2	5	5	4	0	1	5	5	5	0	0	5
Gross behavioral changes[f]																																			
depress. exploration		−	−	+	+	−	−	−	−	+	+	−	−	−	+	+	+	+	−	−	−	−	+	−	−	+	+	−	−	−	−	+	−	+	+	+
body posture		−	−	+	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	+	−	+
passivity		−	−	−	−	−	−	−	+	+	−	+	−	−	−	−	+	−	−	−	−	−	+	+	−	−	−	+	+	−	−	−	−	+	−
vocalization		−	−	+	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	+
restlessness		−	−	−	−	+	−	+	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+
ptosis		+	−	−	+	+	−	−	−	+	+	−	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	+	−	+	+	−	−	+
convulsion		−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	+	−	−	−	−	−	−	−	−	−	−	−
tremor		−	−	+	−	+	−	−	−	−	−	−	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−
motor ataxia		−	−	−	+	−	−	−	−	−	−	−	−	−	−	+	+	−	−	−	−	−	−	−	−	−	+	−	−	−	−	+	+	−	−	+
exophthalmos		−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−
urination		−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	+	+	−	+	−	−	−	−
defecation		+	−	−	+	−	−	−	−	+	+	+	−	−	+	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−

a) aminopyrine *b*) phenylbutazone *c*) benzydamine
d) Number of inhibitions observed in five mice at respective doses. The fraction signifies the number of inhibitions to survivors.
e) The number of fatalities among five tested mice are shown with each dose.
f) The resultant symptoms are indicated as + or −.

11) G. Palazzo and V. Rosnati, *Gazz. Chim. Ital.*, **82**, 584 (1952).
12) E.F. Schmitt, *Chem. Ber.*, **21**, 1811.
13) P.L. Julian and H.C. Printy, *J. Am. Chem. Soc.*, **71**, 3206 (1949).

Pharmacology

Thirty one compounds prepared in this study were screened for their inhibitory action against acetic acid-induced writhing syndrome as the preliminary test for their antiphlogistic-analgesic activity. Their acute toxicity and influence on the general behavior were also investigated. They were compared with standard substances, namely aminopyrine, phenylbutazone and benzydamine for their pharmacological features. The method of pharmacological tests were reported in our earlier paper[14] in detail.

Anti-writhing Activity

Anti-writhing activity of these derivatives was assessed by their inhibition of writhing or streching syndrome in the hind paw of the mouse by injecting acetic acid. A group of 5 male mice (dd strain) in the weight range of 18—22 g were used for each dosage level. The test drugs were administered intraperitoneally to the group at a logarithmic series of doses, ranging from 25 to 100 mg/kg, and 30 minutes later each mouse was injected intraperitoneally with acetic acid (0.5% soln., 0.1 ml/10 g) and were observed for 15 minutes. When streching or writhing syndrome was not observed, the substance tested was considered effective at a specific dose.

Acute Toxicity and Influence on Gross Behavior

After administration of the test drug *i.p.* at different dosage, ranging from 50 to 200 mg/kg, to a group of 5 male mice (dd strain) in the weight range of 18—22 g, gross behavioral changes were observed for 30 minutes continuously, then at intervals of 30 minutes for 2 hours. Mortalities within 48 hours after injection were recorded for respective dose.

The results are summarized in Table VI.

Result and Discussion

As can be seen in Table VI, an anti-writhing activity was found in almost all of the compounds tested, but concurrently they exerted relatively high toxicity.

3-Alkoxy-1[ω-(N-alkylamino)alkyl]-3-phenylindolin-2-ones (4a—g)

Compounds (**4b**) and (**4f**) showed a moderate anti-writhing effect, and were approximately equipotent to aminopyrine. Compound (**4c**) possessed relatively high activity equipotent to or more than phenylbutazone. It seems that LD_{50} values of these compounds are located between 100 mg/kg to 200 mg/kg, *i.p.* (aminopyrine: 288 mg/kg, *i.p.*), therefore they have comparatively high toxicity. As for the effects on gross behavioral changes, various symptoms listed in Table VI were observed for these compounds. However, these symptoms were not specific, it appears that there exists no CNS activity in these compounds.

3-Alkoxy-1[ω-(N,N-dialkylamino)alkyl]-3-phenylindolin-2-ones (5a—p)

Compounds (**5a—c,e,f,h,p**) exerted marked anti-writhing activity, being equal to or better than aminopyrine or phenylbutazone as for this activity, above all, **5f** was the most active of the series. Some of analogues (**5**) also provided relatively high toxicity, but **5a—f** exhibited low toxicity unlike others in the series. As to the effects on gross behavioral changes, various symptoms were observed, but were not specific to exert the effect on CNS.

1[ω-(N,N-Dialkylamino)alkyl]-3-phenylindolin-2-ones (6a—h)

Analogues (**6**) also exhibited anti-writhing activity, but they were more toxic than analogues (**4**) and (**5**) with the exception of (**6d,e**). Compound (**6e**) provided potent anti-writhing activity and relatively low toxicity.

14) S. Toyoshima, N. Hirose, K. Yamatsu, and S. Sohda, *Yakugaku Zasshi*, **90**, 1524 (1970).

From the point of view of the relationship between anti-writhing activity and acute toxicity, **4a—c,f** and **6e** are worth further investigation for their antiphlogistic-analgesic activity. For experimental convenience, the preliminary screening test was carried intraperitoneally for anti-writhing syndrome activity in this study. Anti-writhing syndrome activity and antiphlogistic-analgesic activity are not always parallel, and as a matter of course oral administration and intraperitoneal administration are not always parallel either. Therefore the compounds selected in preliminary screen should be tested orally for their antiphlogistic-analgesic activity as a future theme. 3-Alkyl analogues (III) were synthesized and screened in the previous report,[1] 3-alkoxy analogues (II) prepared in this study were compared with (III) for their pharmacological features. However, they exhibited similar biological profiles. It seems that change of the substituent at position 3 produced no significant effect, and change in the alkyl group represented by R_1 exerted no marked effect on anti-writhing potency. With respect to 1-(N-substituted amino)alkyl group, replacement of the N-substituents represented by R_2 and R_3 resulted in no marked change on biological activity. When the length of alkylene chain signified with *n* was changed from 2 to 3, a marked influence on the activity was not observed.

Experimental[15]

3-Alkoxy-3-phenylindolin-2-ones (2a,b)——To a stirred solution of 3-hydroxy-3-phenylindolin-2-ones 56.3 g (0.25 mole) in 350 ml of dry chloroform was added dropwise a solution of thionyl chloride 149 g in 150 ml of dry chloroform under cooling at 15°. After addition was completed, the mixture was stirred and refluxed for 6 hr, cooled and concentrated to give 70.5 g of crude 3-chloro-3-phenylindolin-2-one (**1**) which was used for the preparation of **2** without further purification. The crude (**1**) was dissolved in 500 ml of appropriate alcohol (MeOH, EtOH), and was heated to reflux for 2 hr. The mixture was concentrated to dryness. The residual oil was dissolved in 150 ml of IPE–$CHCl_3$ (1: 1) mixture, and allowed to stand overnight in refrigerator. 3-Alkoxy-3-phenylindolin-2-ones (**2a,b**) was obtained as colorless needles after recrystallization from EtOAc.

3-Methoxy-3-phenylindolin-2-one (**2a**): mp 170—171°, colorless needles (from EtOAc). Yield 52.4%. IR ν_{max}^{Nujol} cm^{-1}: 3250(secondary amide NH), 1705(secondary amide C=O). NMR ($CDCl_3$, TMS) δ: 3.28 ppm (3H, singlet, OCH_3), 6.8—7.3 (9H, multiplet, aromatic H), 9.48(1H, broad singlet, secondary amide NH). *Anal.* Calcd. for $C_{15}H_{13}O_2N$: C, 75.31; H, 5.48; N, 5.85. Found: C, 75.03; H, 5.60; N, 5.91.

2-Ethoxy-3-phenylindolin-2-one (**2b**): mp 169—170°; colorless needles (from EtOAc). Yield 63.5%. IR ν_{max}^{Nujol} cm^{-1}: 3250 (secondary amide NH), 1700 (secondary amide C=O). NMR ($CDCl_3$, TMS) δ: 1.29 ppm (3H, triplet, J=8 Hz, $OCH_2\underline{CH_3}$), 3.40 (2H, quartet, J=8 Hz, $OC\underline{H_2}Me$), 6.8—7.3 (9H, multiplet, aromatic H), 9.50 (1H, broad singlet, secondary amide NH). *Anal.* Calcd. for $C_{16}H_{15}O_2N$: C, 75.87; H, 5.97; N, 5.53. Found: C, 76.02; H, 5.86; N, 5.78.

3-Alkoxy-1(ω-chloroalkyl)-3-phenylindolin-2-ones (3a—d)——To a suspension of **2** (0.05 mole) in 150 ml of dry toluene was added sodium amide 2.4 g (0.06 mole). After the mixture was stirred for 1.5 hr at room temperature, appropriate ω-chloroalkyl bromide (0.06 mole) was added. The reaction mixture was stirred and refluxed for 7 hr, diluted with ice-water, and extracted with benzene. After being dried, the extracts were concentrated, and the residue was purified by recrystallization or distillation to give (**3a—d**). Physical properties and results of microanalysis are listed in Table I.

3-Alkoxy-1[ω-(N-alkylamino)alkyl]-3-phenylindolin-2-ones (4a—g)——Amixture of **3** (0.02 mole) and a large excess of appropriate amine (40 ml of 30% $MeNH_2$ or $EtNH_2$ ethanol solution) was heated in autoclave at 100° for 10 hr, evaporated under reduced pressure, and diluted with water. After extracting with ether, the water layer was made alkaline with 10% NaOH, and oil separated was extracted with ether to give crude product, which was purified by distillation and converted into the salt indicated in Table II.

3-Alkoxy-1[ω-(N,N-dialkylamino)alkyl]-3-phenylindolin-2-ones (5a—p)——a) A mixture of 3 (0.02 mole) and excess of appropriate amine (0.06 mole of amine in 40 ml of EtOH) was treated as described for the preparation of **4**. The product, if an oil, was purified by distillation; if solid, it was refined by recrystallization. Compounds (**5c,d,g,h,k,l,o,p**) were prepared by this procedure.

b) A suspension of **2** (0.02 mole) and sodium amide 0.86 g (0.022 mole) in 60 ml of dry xylene was stirred for 1 hr at ordinary temperature, and ω(N,N-dialkylamino)alkyl chloride (0.025 mole) was added. The

15) Melting points and boiling points were uncorrected. IR spectra were determined on Hitachi-215 spectrometer and NMR spectra on a Japan Electron Optics Model JNM-PS 100 spectrometer. The mass spectra were recorded on JMS-01 SG spectrometer.

mixture was stirred and heated to reflux for 6 hr, diluted with ice-water and extracted with ether. The ethereal extract was extracted with 2N HCl. The acid extracts were made alkaline with conc. NaOH, and the oil separated was extracted with ether. After being dried, the ether extracts were concentrated and the residue was distilled under diminished pressure. Compounds (**5a,b,e,f,i,j,m,n**) were prepared by this method, and converted into the salts indicated in Table II.

1[ω-(N,N-dialkylamino)alkyl]-3-phenylindolin-2-ones (6a—h)——To a stirred solution of **5** (0.02 mole) in 150 ml of dry benzene was added dropwise a solution of $NaAlH_2(OCH_2CH_2OCH_3)_2$ 12.6 g (64% solution in benzene) in 15 ml of dry benzene at room temperature. The reaction mixture was stirred and refluxed for 4 hr, then 5 ml acetone was added at room temperature to decompose the excess of reducing reagent, and 10% NaOH was added. The mixture was extracted with benzene, the extracts were dried and evaporated. The oily residue was distilled to give pure amine. The free amines obtained were converted to appropriate salts listed in Table III.

General Method of Preparation of (7c, d, 2h)——To a stirred solution of the secondary amide (**7a, b, 2e**) (0.1 mole) in 100 ml of dry benzene was added portionwise NaH (50% mineral oil dispersion) 5.3 g at room temperature. After stirring for 30 min alkyl iodide (MeI or EtI) was added dropwise to the mixture, and then heated to reflux for 5 hr. The mixture was added to 200 ml of cold water and extracted with benzene. After drying, removal of solvent yielded pale yellow viscous liquid. The crude products were purified by recrystallization or distillation.

1,3-Dimethyl-3-phenylindolin-2-one (**7c**): bp 143—145° (0.3 mmHg), Yield 9.7 g (82%).

1,3-Diethyl-3-phenylindolin-2-one (**7d**): mp 80—82° (columns from IPE), Yield 10.5 g (79%).

3-Methoxy-1-methyl-3-phenylindolin-2-one (**2h**): mp 83—84° (blades from IPE), Yield 11.5 g (91%). IR ν_{max}^{Nujol} cm^{-1}: 1695 (tert. amide C=O). NMR ($CDCl_3$, TMS) δ: 3.25 ppm (3H, singlet, N-CH_3), 3.30 (3H, singlet, OCH_3), 6.8—7.6 (9H, multiplet, aromatic H). *Anal.* Calcd. for $C_{16}H_{15}O_2N$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.91; H, 6.02; N, 5.31.

Reduction of (7a—d, 2e—h) with $NaAlH_2(OCH_2CH_2OCH_3)_2$——To a stirred solution of (**7a—d, 2e—h**) (0.02 mole) in 100 ml of dry benzene was added dropwise a solution of corresponding amount of $NaAlH_2(OCH_2CH_2OCH_3)_2$ (0.02 mole or 0.06 mole) in 20 ml of dry benzene at room temperature. After addition was completed, the mixture was stirred and refluxed for 2 hr, then cooled to 10°. Acetone 5 ml was added to the mixture for decomposing the excess of reagent, then 10% NaOH was added, and the mixture was extracted with ether. The ethereal extract was dried and concentrated to give crude product, which was purified by column chromatography on silica gel. Elution with IPE yielded pure product. The product was purified further by recrystallization or distillation.

1,3-Dimethyl-3-phenylindoline (**9c**): bp 135—140° (0.8 mmHg), colorless liquid, yield 72%. NMR (CCl_4, TMS) δ: 1.50 ppm (3H,singlet, C_3-CH_3), 2.53 (3H, singlet, N-CH_3), 3.20 (2H, AB-quartet, J=8 Hz, δ_{AB}=10 Hz, C_2-geminal H), 6.3—7.3 (9H, multiplet, aromatic H). Mass Spectrum *m/e*: 223 (M^+), 208 (base peak), 193, 163. *Anal.* Calcd. for $C_{16}H_{17}N$: C, 86.05; H, 7.67; N, 6.27. Found: C, 85.80; H, 7.65; N, 6.42.

1,3-Diethyl-3-phenylindoline (**9d**): bp 137—139° (0.3 mmHg), pale yellow liquid, yield 84%. NMR (CCl_4, TMS) δ: 0.81 ppm (3H, triplet, J=8 Hz, C_3-$CH_2C\underline{H}_3$), 1.10 (3H, triplet, J=8 Hz, N-$CH_2C\underline{H}_3$), 2.05 (2H, quartet, J=8 Hz, C_3-$C\underline{H}_2Me$), 3.10 (2H, quartet, J=8 Hz, N-$C\underline{H}_2Me$), 3.36 (2H, singlet, C_2-geminal H), 6.3—7.4 (9H, multiplet, aromatic H). Mass Spectrum *m/e*: 251 (M^+), 236, 222 (base peak), 193, 165. *Anal.* Calcd. for $C_{18}H_{21}N$: C, 86.01; H, 8.42; N, 5.57. Found: C, 85.81; H, 8.64; N, 5.32.

2-Hydroxy-1,3-dimethyl-3-phenylindoline (**8c**): mp 93—95°, colorless prisms (from IPE), yield 75%. IR ν_{max}^{Nujol} cm^{-1}: 3300 (OH). NMR (DMSO-d_6, TMS) δ: 1.58 ppm (3H, singlet, C_3-CH_3), 2.70 (3H, singlet, N-CH_3), 4.79 (1H, doublet, J=7 Hz, C_2-H), 5.95 (1H, doublet, J=7 Hz, C_2-OH), 6.4—7.4 (9H, multiplet, aromatic H); (DMSO-d_6+D_2O, TMS) δ: 1.58 ppm (3H, singlet, C_3-CH_3), 2.70 (3H, singlet, N-CH_3), 4.82 (1H, singlet, C_2-H), 6.4—7.4 (9H, multiplet, aromatic H); ($CDCl_3$, TMS) δ: 1.59, 1.71 (3H, two singlets, relative intensity ratio 1: 1, C_3-CH_3), 2.0 (1H, broad, C_3-OH), 2.77 (3H, singlet, N-CH_3), 4.60, 4.80 (1H, two singlets, relative intensity ratio 1: 1 ,C_2-H), 6.4—7.4 (9H, multiplet, aromatic H). Mass Spectrum *m/e*: 239 (M^+, base peak), 224, 222, 210, 194, 165, 152, 146, 134. *Anal.* Calcd. for $C_{16}H_{17}ON$: C, 80.30; H, 7.16, N, 5.85. Found: C, 80.16; H, 6.86, N, 5.70.

2-Hydroxy-1,3-diethyl-3-phenylindoline (**8d**): bp 154—157° (0.9 mmHg), pale yellow viscous liquid, yield 85%. IR $\nu_{max}^{Liqfilm}$ cm: 3320 (OH). NMR ($CDCl_3$, TMS) δ: 0.82, 0.88 ppm (3H, two overlapped triplets, J=8 Hz, C_3-$CH_2C\underline{H}_3$), 1.15 1.20 (3H, two overlapped triplets, J=8 Hz, N-$CH_2C\underline{H}_3$), 2.0 (1H, broad, OH), 2.10,2.22 (2H, two overlapped quartets J=8, Hz, C_3-$C\underline{H}_2Me$), 3.38, 3.48 (2H, two overlapped quartets, J= 8 Hz, N-$C\underline{H}_2Me$), 4.9, 5.0 (1H, two broad singlets, C_2-H), 6.5—7.5 (9H, multiplet, aromatic H). Mass Spectrum *m/e*: 267 (M^+), 238 (base peak), 236, 222, 208, 193, 165, 160, 152, 148. *Anal.* Calcd. for $C_{18}H_{21}ON$: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.83; H, 8.08; N, 5.43.

2-Hydroxy-3-methoxy-1-methyl-3-phenylindoline (**10h**): mp 94—95°, colorless needles (from IPE), yield 72%. IR ν_{max}^{Nujol} cm^{-1}: 3420 (OH). NMR ($CDCl_3$, TMS) δ: 2.81 ppm (3H, singlet, N-CH_3), 3.20 (3H, singlet, OCH_3), 3.4 (1H, broad, OH), 4.5 (1H, singlet, C_2-H), 6.6—7.6 (9H, multiplet, aromatic H). Mass Spectrum *m/e*: 255 (M^+, base peak), 240, 224, 222, 212, 194, 165, 152, 146, 134. *Anal.* Calcd. for $C_{16}H_{17}O_2N$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.51; H, 6.70; N, 5.67.

1-Methyl-3-phenylindolin-2-one (11h)[11]: mp 120°, blades (from IPE). NMR ($CDCl_3$, TMS) δ: 3.17 ppm (3H, singlet, N-CH_3), 4.47 (1H, singlet, C_3-H), 6.6—7.5 (9H, multiplet, aromatic H). IR ν_{max}^{MeOH} cm^{-1}: 1695 (amide C=O). *Anal.* Calcd. for $C_{15}H_{13}ON$: C, 80.67; H, 5.87; N, 6.27. Found: C, 80.69; H, 5.64; N, 6.20.

3-Phenylindolin (12)[12]: mp 88—89°, scales (from light petroleum), yield: 63% (from **2e**), 59% (from **2f**), and 48% (from **2g**). IR ν_{max}^{Nujol} cm^{-1}: 3425

Reduction of 8c to 9c with $NaAlH_2(OCH_2CH_2OCH_3)_2$——To a solution of **8c** 2.4 g in 50 ml of dry benzene was added 6.5 g of $NaAlH_2(OCH_2CH_2OCH_3)_2$ (64% benzene solution) at room temperature. The mixture was stirred and heated to reflux for 7 hr, then 5 ml of acetone was added. After addition of 10% NaOH the mixture was extracted with benzene, the extracts were dried and evaporated. The oily residue was distilled to give 1.7 g of colorless liquid: bp 136—140° (0.8 mmHg), which was identified with **9c** by means of IR and NMR spectrum.

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