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# Studies on Benzoheterocyclic Derivatives. XII.[1] Synthesis and Pharmacological Actions of Indoline Derivatives. (3)

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A total of 39 derivatives of 3-alkyl-1-[*w*-(N-substituted amino)alkyl]-3-phenylindolin-2-ones and their related compounds were synthesized for pharmacological testing. Compounds were tested for analgetic-antiphlogistic activity by anti-writhing tests in mice. Acute toxicity and effects upon the general behaviour in mice were also determined.

Previously we reported[1,3] synthesis of 1-phenylindolin-2-one (I) and 1-benzylindolin-2-one (II) derivatives containing N-substituted aminoalkyl group at position 3 of indoline ring. We also described their inhibitory activity against acetic acid-induced writhing syndrome, and discussed their structure-activity relationship.

It was concluded that some of these derivatives possessed significant anti-writhing syndrome activity, but they possessed relatively high toxicity. The antiphlogistic-analgesic activities of these compounds against Carrageenin or Kaolin-induced edema are being investigated at our laboratories.

In this paper, we describe the influence of the reciprocal shift between N-substituted aminoalkyl group and phenyl group at positions 1 and 3 of I on the pharmacological activities and toxicity. We synthesized 3-alkyl-1-[$\omega$(N-substituted amino)alkyl]-3-phenylindolin-2-ones (III). We also synthesized 1-[$\omega$(N-substituted amino)alkyl]-3-phenylindolines (IV) which were reduced forms of III analogs.

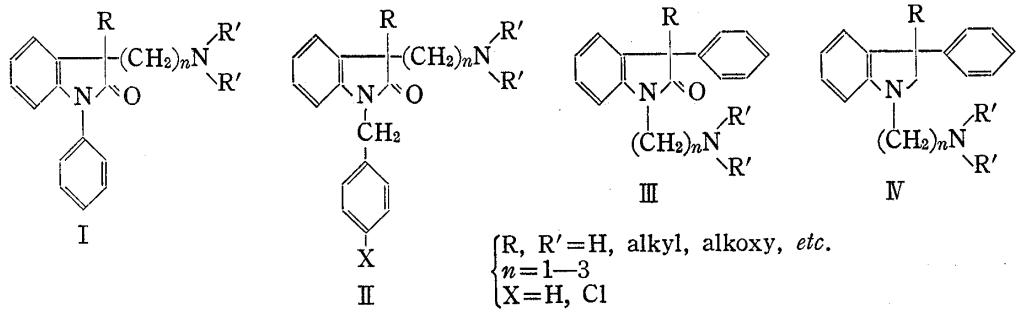



Chart 1

## Chemistry

The general synthetic scheme used in the preparation of these compounds is illustrated in Chart 2.

3-Alkyl-3-phenylindolin-2-ones (**1**) were prepared by treating 3-phenylindolin-2-one[4] with one equivalent of sodium hydride and corresponding alkyl iodide in dimethylformamide solution. Excess molar alkylating reagents brought on the production of 1,3-dialkylated

1) Part XI: N. Hirose, S. Sohda, and S. Toyoshima, *Yakugaku Zasshi*, **91**, 1323 (1971).
2) Location: *Koishikawa 4-6-10, Bunkyo-ku, Tokyo.*
3) Part VIII: S. Toyoshima, N. Hirose, K. Yamatsu, and S. Sohda, *Yakugaku Zasshi*, **90**, 1524 (1970).
4) J. Meisenheimer and H. Meis, *Chem. Ber.*, **57B**, 289 (1924).

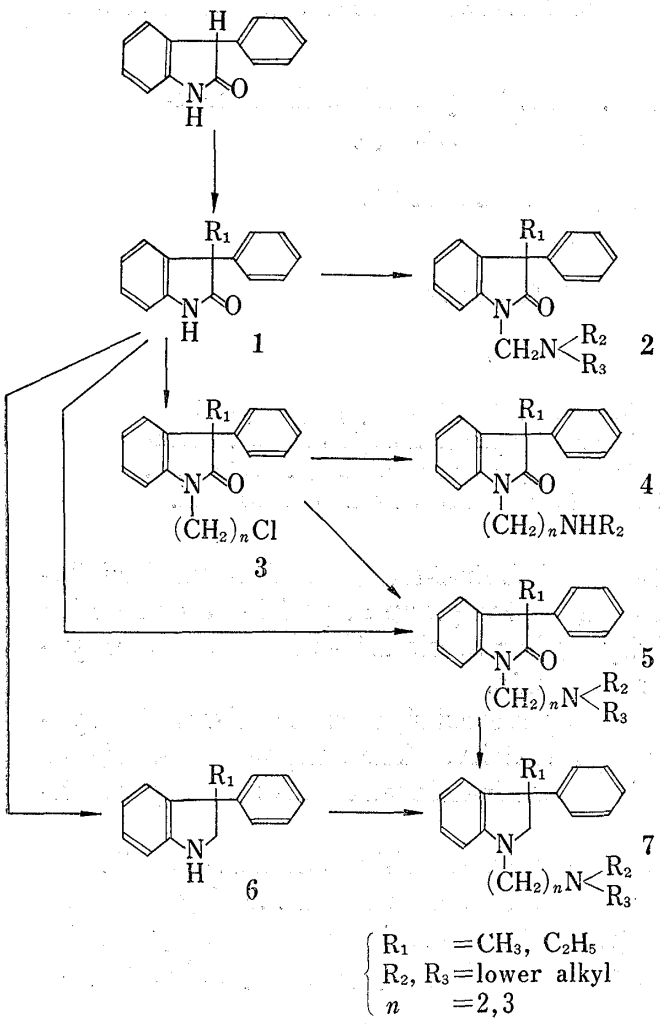



Chart 2

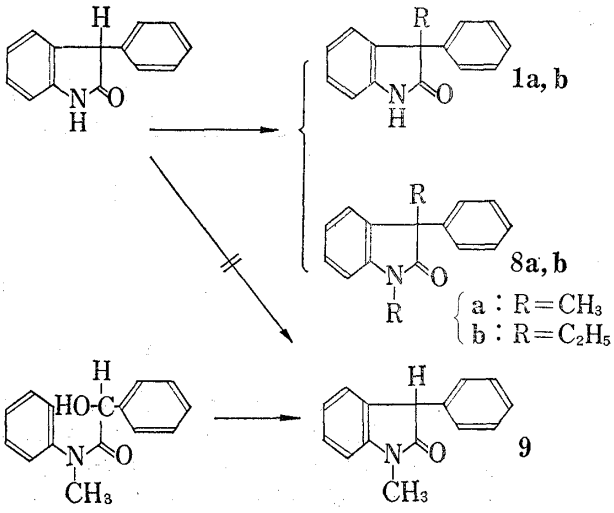



Chart 3

products (**8**). A position of the alkyl group introduced was verified at position 3 by Bruce, *et al.*,[5] *via*, 3-methyl-3-phenylindolin-2-one (**1a**) was obtained from N-phenyl-N'-α-phenylpropionylhydrazine in poor yield, and was shown to be identical with the methylation product of 3-phenylindolin-2-one.

1-Methyl-3-phenylindolin-2-one[5,6] (**9**) which was 1-methylated isomer of **1** was synthesized from N-methylmandelanilide.[7] In comparison with infrared (IR) and nuclear magnetic resonance (NMR) spectrum of both the isomers (**1a** and **9**), the alkyl group of **1** was confirmed to be located at position 3.

3-Methyl-3-phenyl-1-piperidinomethylindolin-2-one (**2**) was obtained by the treatment of **1** with paraformaldehyde and piperidine hydrochloride by way of modified Mannich reaction.[8] 3-Alkyl-1-(ω-chloroalkyl)-3-phenylindolin-2-ones (**3**) were prepared by the reaction with **1**, corresponding ω-chloroalkyl bromide and sodium hydride. Reaction of **3** with an excessive amount of monoalkyl amine produced alkyl-1-[ω(N-alkylamino)alkyl]-3-phenylindolin-2-ones (**4**), and with dialkyl amine produced 3-alkyl-1-[ω(N,N-dialkylamino)alkyl]-3-phenylindolin-2-ones (**5**). Compounds (**5**) were also obtained by the alkylation of **1** with appropriate ω(N,N-dialkylamino)alkyl chlorides in the presence of sodium amide.[9]

Reduction of **1** with sodium dihydro-bis(2-methoxyethoxy)-aluminate or lithium aluminum hydride[10] conceded good yield of 3-alkyl-3-phenylindoline (**6**). Alkylation of **6** with ω(N,N-dialkylamino)alkyl chlorides yielded corresponding 3-alkyl-1-[ω(N,N-dialkylamino)-alkyl]-3-phenylindolines (**7**). Compounds (**7**) were also obtained by the reduction of **5** with sodium dihydro-bis(2-methoxyethoxy)-aluminate.

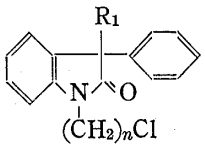
5) *a*) J.M. Bruce and F.K. Sttcliffe, *J. Chem. Soc.*, **1957**, 4789; *b*) J.M. Bruce, P. Knowles, and L.S. Besford, *ibid.*, **1964**, 4044.
6) G.N. Walker, R.T. Smith, and B. Weaver, *J. Med. Chem.*, **8**, 626 (1965).
7) G. Palazzo and V. Rosnati, *Gazz. Chim. Ital.*, **82**, 584 (1952).
8) H. Zinner and H. Wigert, *Chem. Ber.*, **94**, 2209 (1961).
9) H.J. Havera, J.W. VanDyke Jr., T.M.H. Liu, and L.F. Sancilio, *J. Med. Chem.*, **12**, 580 (1969).

Physical properties, formula, yield and results of elementary analysis of the synthesized compounds are summarized in Table I—IV.

## Pharmacology

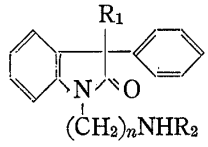
Prior to the investigation of the antiphlogistic-analgesic activity against Carrageenin or Kaolin-induced edema, 39 compounds synthesized in this study were screened for their inhibitory action[11] against acetic acid induced writhing syndrome as the preliminary screening

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 | (128—129) | 68.4 | $C_{17}H_{16}ONCl$ | scales (IPA) | 71.44 | 5.65 | 4.90 | 71.74 | 5.70 | 4.97 |
| **3b** | $CH_3$ | 3 | 187—189/0.4 | 64.9 | $C_{18}H_{18}ONCl$ | viscous oil | 72.10 | 6.05 | 4.67 | 71.82 | 6.25 | 4.76 |
| **3c** | $C_2H_5$ | 2 | (110—111) | 70.3 | $C_{18}H_{18}ONCl$ | needles (IPE) | 72.10 | 6.05 | 4.67 | 72.07 | 6.12 | 4.70 |
| **3d** | $C_2H_5$ | 3 | 189—191/0.5 | 59.6 | $C_{19}H_{20}ONCl$ | viscous oil | 72.71 | 6.44 | 4.46 | 73.01 | 6.65 | 4.68 |

Table II.[a] 3-Alkyl-1-[ω(N-alkylamino)alkyl]-3-phenylindolin-2-ones (4)



| Compd. No. | $R_1$ | $R_2$ | $n$ | bp (°C/mmHg) | Yield (%) | Formula (salt) | mp (°C)[b] | Analysis (%) Calcd. C | H | N | Found C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **4a** | $CH_3$ | $CH_3$ | 2 | 188—190/0.5 | 72.5 | $C_{18}H_{20}ON_2$ HCl | 225—227 needles | 68.22 | 6.69 | 8.44 | 67.93 | 6.66 | 8.88 |
| **4b** | $CH_3$ | $C_2H_5$ | 2 | 170—171/0.4 | 76.4 | $C_{19}H_{20}ON_2$ HCl | 167—169 needles | 68.96 | 7.02 | 8.47 | 68.76 | 7.08 | 8.20 |
| **4c** | $CH_3$ | $C_2H_5$ | 3 | 175—176/0.7 | 68.9 | $C_{20}H_{24}ON_2$ HCl | 202—203 needles | 69.94 | 7.32 | 8.12 | 69.79 | 7.21 | 8.09 |
| **4d** | $C_2H_5$ | $CH_3$ | 2 | 185—187/0.5 | 79.1 | $C_{19}H_{22}ON_2$ HCl | 229—230 needles | 68.96 | 7.02 | 8.47 | 68.71 | 6.93 | 8.36 |
| **4e** | $C_2H_5$ | $C_2H_5$ | 2 | 190—196/0.6 | 71.9 | $C_{20}H_{24}ON_2$ HCl | 188—190 needles | 69.64 | 7.32 | 8.12 | 69.10 | 7.36 | 8.17 |
| **4f** | $C_2H_5$ | $C_2H_5$ | 3 | 199—200/0.5 | 74.3 | $C_{21}H_{26}ON_2$ HCl | 195—197 needles | 70.26 | 7.60 | 7.81 | 70.15 | 7.55 | 7.79 |

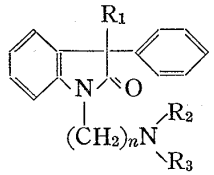
*a*) On table II, III, and IV, $C_4H_4O_4$(M), $C_4H_4O_4$ (F), and $C_2H_2O_4$ represent respectively maleic acid, fumalic acid and oxalic acid. The compounds listed in the formula column were used for microanalysis and pharmacological screening tests.

*b*) recrysted from isopropanol

10) P.L. Julian and H.C. Printy, *J. Am. Chem. Soc.*, **71**, 3206 (1949).

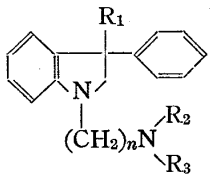
11) R. Koster, *Fed. Proc.*, **18**, 412 (1959).

TABLE III. 3-Alkyl-1-[ω(NN,N-dialkylamino)alkyl]-3-phenylindolin-2-ones (**5**)



| Compd. No. | $R_1$ | $R_2$ | $R_3$ | $n$ | bp(°C/mmHg) (mp °C) | Yield (%) | Formula (salt) | mp (°C) | Analysis (%) Calcd. C | Calcd. H | Calcd. N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **5a** | $CH_3$ | $CH_3$ | $CH_3$ | 2 | 154—155/0.1 | 84.7 | $C_{19}H_{22}ON_2$ HCl | 186—188 needles | 68.96 | 7.02 | 8.47 | 68.74 | 7.00 | 8.22 |
| **5b** | $CH_3$ | $C_2H_5$ | $C_2H_5$ | 2 | 173—175/0.4 | 86.4 | $C_{21}H_{26}ON_2$ HCl | 149—151 needles | 70.26 | 7.60 | 7.81 | 70.20 | 7.71 | 7.73 |
| **5c** | $CH_3$ | $(CH_2)_5$ | | 2 | 190—195/0.4 | 78.3 | $C_{22}H_{26}ON_2$ HCl | 155—157 needles | 71.23 | 7.35 | 7.55 | 71.06 | 7.48 | 7.44 |
| **5d** | $CH_3$ | $(CH_2)_2O(CH_2)_2$ | | 2 | (93—95) | 87.9 | $C_{21}H_{24}O_2N_2$ HCl | 206—207 needles | 67.65 | 6.71 | 7.51 | 67.17 | 6.70 | 7.84 |
| **5e** | $CH_3$ | $CH_3$ | $CH_3$ | 3 | 176—180/0.8 | 79.1 | $C_{20}H_{24}ON_2$ $C_2H_2O_4$ | 175—176 needles | 66.31 | 6.58 | 7.03 | 66.12 | 6.69 | 6.98 |
| **5f** | $CH_3$ | $C_2H_5$ | $C_2H_5$ | 3 | 184—185/0.5 | 80.6 | $C_{22}H_{28}ON_2$ $C_2H_2O_4$ | 128—129 needles | 67.58 | 7.09 | 6.57 | 67.24 | 7.13 | 6.62 |
| **5g** | $CH_3$ | $(CH_2)_5$ | | 3 | 210—216/0.8 | 78.8 | $C_{23}H_{23}ON_2$ $C_4H_{34}O_4$(M) | 120—121 prisms | 69.80 | 6.94 | 6.03 | 69.53 | 6.83 | 6.23 |
| **5h** | $CH_3$ | $(CH_2)_2O(CH_2)_2$ | | 3 | 220—221/1.4 | 77.3 | $C_{22}H_{26}O_2N_2$ $C_4H_4O_4$(M) $\frac{1}{2}H_2O$ | 128—129 needles | 64.13 | 6.52 | 6.23 | 64.44 | 6.63 | 6.16 |
| **5i** | $C_2H_5$ | $CH_3$ | $CH_3$ | 2 | 170—171/0.4 | 78.4 | $C_{20}H_{24}ON_2$ HCl $\frac{1}{2}H_2O$ | 87— 89 needles | 68.74 | 7.37 | 8.02 | 68.56 | 7.14 | 8.27 |
| **5j** | $C_2H_5$ | $C_2H_5$ | $C_2H_5$ | 2 | 188—190/0.7 | 80.2 | $C_{22}H_{28}ON_2$ HCl | 188—189 needles | 70.84 | 7.85 | 7.51 | 71.00 | 7.76 | 7.74 |
| **5k** | $C_2H_5$ | $(CH_2)_5$ | | 2 | 192—194/0.4 | 76.5 | $C_{23}H_{28}ON_2$ HCl | 263—265 needles | 71.75 | 7.61 | 7.28 | 71.63 | 7.47 | 7.52 |
| **5l** | $C_2H_5$ | $(CH_2)_2O(CH_2)_2$ | | 2 | (75—77) | 86.3 | $C_{22}H_{26}O_2N_2$ HCl | 228—230 needles | 68.28 | 7.05 | 7.24 | 68.09 | 6.93 | 7.24 |
| **5m** | $C_2H_5$ | $CH_3$ | $CH_3$ | 3 | 173—175/0.3 | 68.5 | $C_{21}H_{26}ON_2$ HCl | 203—204 needles | 70.26 | 7.60 | 7.81 | 70.27 | 7.56 | 8.07 |
| **5n** | $C_2H_5$ | $C_2H_5$ | $C_2H_5$ | 3 | 191—192/0.6 | 79.7 | $C_{23}H_{30}ON_2$ HCl | 164—166 needles | 71.38 | 8.09 | 7.24 | 71.08 | 7.97 | 7.44 |
| **5o** | $C_2H_5$ | $(CH_2)_5$ | | 3 | 209—212/0.6 | 75.9 | $C_{24}H_{30}ON_2$ HCl | 224—225 needles | 72.24 | 7.85 | 7.02 | 71.95 | 7.76 | 7.12 |
| **5p** | $C_2H_5$ | $(CH_2)_2O(CH_2)_2$ | | 3 | 227—228/1.0 | 78.6 | $C_{23}H_{28}O_2N_2$ HCl | 207—209 needles | 68.89 | 7.30 | 6.99 | 69.12 | 7.33 | 7.23 |

TABLE IV. 3-Alkyl-1-[ω(N,N-dialkylamino)alkyl]-3-phenylindolines (7)



| Compd. No. | $R_1$ | $R_2$ | $R_3$ | $n$ | bp (°C/mmHg) | Yield (%) | Formula (salt) | mp (°C) | Analysis (%) Calcd. C | Calcd. H | Calcd. N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **7a** | $CH_3$ | $CH_3$ | $CH_3$ | 2 | 148—150/0.2 | 83.5 | $C_{19}H_{24}N_2$ $C_4H_4O_4$(M) | 122—124 | 69.66 | 7.13 | 7.07 | 69.26 | 7.24 | 6.42 |
| **7b** | $CH_3$ | $C_2H_5$ | $C_2H_5$ | 2 | 164—165/0.4 | 80.2 | $C_{21}H_{28}N_2$ 2 HCl | 150—152 | 66.12 | 7.94 | 7.35 | 66.15 | 7.89 | 7.46 |
| **7c** | $CH_3$ | $(CH_2)_5$ | | 2 | 165—166/0.2 | 75.4 | $C_{22}H_{28}N_2$ $C_4H_4O_4$(F) | 172—173 | 71.52 | 7.40 | 6.41 | 71.78 | 7.43 | 6.42 |
| **7d** | $CH_3$ | $(CH_2)_2O(CH_2)_2$ | | 2 | 180—182/0.4 | 76.9 | $C_{21}H_{26}N_2O$ $C_2H_2O_4$ | 173—174 | 66.95 | 6.36 | 6.79 | 66.76 | 6.65 | 6.57 |
| **7e** | $CH_3$ | $CH_3$ | $CH_3$ | 3 | 162—163/0.4 | 74.6 | $C_{20}H_{26}N_2$ $2HCl \cdot H_2O$ | 186—188 | 62.32 | 7.86 | 7.27 | 62.51 | 7.91 | 7.24 |
| **7f** | $CH_3$ | $C_2H_5$ | $C_2H_5$ | 3 | 173—176/0.5 | 70.3 | $C_{22}H_{30}N_2$ 2 HCl | 162—164 | 66.81 | 8.17 | 7.09 | 66.94 | 8.28 | 7.09 |
| **7g** | $CH_3$ | $(CH_2)_5$ | | 3 | 188—189/0.4 | 82.5 | $C_{23}H_{30}N_2$ $C_4H_4O_4$(M) | 122—124 | 71.96 | 7.62 | 6.21 | 72.17 | 7.78 | 6.11 |
| **7h** | $CH_3$ | $(CH_2)_2O(CH_2)_2$ | | 3 | 200—202/0.4 | 81.6 | $C_{22}H_{30}N_2O$ $C_4H_4O_4$(M) | 139—140 | 68.99 | 7.14 | 6.19 | 68.82 | 7.05 | 6.21 |
| **7i** | $C_2H_5$ | $CH_3$ | $CH_3$ | 2 | 146—149/0.3 | 77.4 | $C_{20}H_{26}N_2$ $C_4H_4O_4$(M) | 108—110 | 70.20 | 7.38 | 6.82 | 70.09 | 7.27 | 6.89 |
| **7j** | $C_2H_5$ | $C_2H_5$ | $C_2H_5$ | 2 | 158—159/0.3 | 80.5 | $C_{22}H_{30}N_2$ $C_4H_4O_4$(F) | 110—112 | 71.19 | 7.82 | 6.38 | 71.32 | 7.79 | 6.70 |
| **7k** | $C_2H_5$ | $(CH_2)_5$ | | 2 | 180—182/0.3 | 76.2 | $C_{23}H_{30}N_2$ $C_2H_2O_4$ | 192—195 | 70.71 | 7.61 | 6.60 | 70.26 | 7.53 | 6.60 |
| **7l** | $C_2H_5$ | $(CH_2)_2O(CH_2)_2$ | | 2 | 180—181/0.4 | 81.4 | $C_{22}H_{28}N_2O$ $C_2H_2O_4$ | 180—181 | 67.57 | 7.10 | 6.57 | 67.21 | 7.13 | 6.69 |
| **7m** | $C_2H_5$ | $CH_3$ | $CH_3$ | 3 | 170—172/0.4 | 82.3 | $C_{21}H_{28}N_2$ $C_4H_4O_4$(M) | 123—125 | 70.71 | 7.61 | 6.59 | 71.00 | 7.76 | 6.68 |
| **7n** | $C_2H_5$ | $C_2H_5$ | $C_2H_5$ | 3 | 172—173/0.3 | 70.9 | $C_{23}H_{32}N_2$ 2 HCl | 173—174 | 67.45 | 8.38 | 6.84 | 67.19 | 8.32 | 6.78 |
| **7o** | $C_2H_5$ | $(CH_2)_5$ | | 3 | 199—200/0.4 | 75.4 | $C_{24}H_{32}N_2$ 2 HCl | 156—158 | 68.38 | 8.15 | 6.64 | 68.34 | 8.28 | 6.51 |
| **7p** | $C_2H_5$ | $(CH_2)_2O(CH_2)_2$ | | 3 | 197—200/0.4 | 79.6 | $C_{23}H_{30}N_2O$ $C_2H_2O_4$ | 153—154 | 68.15 | 7.34 | 6.36 | 68.20 | 7.43 | 6.49 |

test, their acute toxicity and influence on the general behavior were also investigated. As the details of pharmacological tests were reported[3] previously, they are described briefly in this paper.

**Anti-writhing Activity**——Anti-writhing activity of these derivatives was assessed by their inhibition of writhing or stretching syndrome in the hind paw of the mouse caused by an injection of acetic acid. A group of 5 male mice (dd strain) weighing 18—22 g were used

TABLE V. Pharmacological Data of Anti-writhing Activity and Acute Toxicity

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

| | Dose mg/kg (*i.p.*) | Compd. No. 7 a | b | c | d | e | f | g | h | i | j | k | l | m | n | o | p |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Anti-writhing activity[a] | 25 | 2 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 1 | 2 | 0 | 5 | 4 | 2 |
| | 50 | 3 | 2 | 5 | 0 | 1 | 2 | 2 | 3 | 3 | 3 | 5 | 5 | 3 | 5 | 5 | 4 |
| | 100 | 5 | 5 | 5 | 4 | 5 | 4/4 | 2/3 | 5 | 5 | 4 | 5 | 3/2 | 5 | 4/4 | 4/4 | 5 |
| Acute toxicity[b] | 50 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 100 | 0 | 0 | 0 | 0 | 0 | 1 | 2 | 0 | 0 | 0 | 0 | 3 | 0 | 1 | 1 | 0 |
| | 200 | 4 | 1 | 5 | 1 | 5 | 5 | 5 | 0 | 1 | 5 | 5 | 2 | 4 | 5 | 5 | 1 |
| Gross behavioral changes[c] | | | | | | | | | | | | | | | | | |
| depress. exploration | | + | + | + | − | + | + | + | − | + | − | + | + | + | − | − | − |
| body posture | | − | − | + | − | − | − | − | − | − | − | + | − | − | − | − | − |
| passivity | | − | + | − | − | − | − | + | − | + | − | + | − | + | − | − | − |
| ptosis | | − | − | − | − | − | − | − | − | − | + | − | − | + | − | − | + |
| restlessness | | − | − | − | − | + | − | − | + | − | − | + | − | − | − | − | − |
| convulsion | | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − |
| tremor | | − | + | − | − | − | − | − | − | − | − | − | − | − | − | − | − |
| motor ataxia | | − | − | − | − | − | − | − | + | − | − | + | − | − | − | − | + |
| exophthalmos | | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − |
| piloelection | | − | − | − | − | − | − | + | − | − | − | − | − | − | − | − | − |
| salivation | | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − |

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

for each dosage level. The substance was administered (*i.p.*) to the group at a logarithmic series of doses, ranging from 25 to 200 mg/kg, and 30 minutes later each mouse was injected (*i.p.*) with acetic acid (0.5%, 0.1 ml/10 g) and were observed for 15 minutes. The substance was considered effective at a specific dose, when stretching or writhing syndrome was not observed.

**Acute Toxicity and Influence on Gross Behavior**——After administration of substance (*i.p.*) at different dosage to a group of 5 male mice (dd strain) weighing 18—22 g, they were observed for the gross behavioral changes for 30 minutes constantly, then at intervals of 30 minutes for 2 hours. Mortalities within 48 hours of the treatment were recorded for respective dose. Observation of the influence on general behavior due to the substance has great significance, for we can roughly predict its activity on the CNS or autonomic nervous system by the investigation of these phenomena.

## Result

In order to investigate the influence of the reciprocal shift between N-substituted amino-alkyl group and phenyl group at positions 1 and 3 of 3-alkyl-3-(N-substituted amino) alkyl-1-phenylindolin-2-ones (I) reported[1] previously, 3-alkyl-1-(N-substituted amino)alkyl-3-phenylindolin-2-ones (III) were synthesized and examined for their phamacological properties. However, no significant influence derived from the shift was observed markedly; III analogs appear to possess pharmacological features similar to that of I analogs.

Anti-writhing activity was found in almost all of the III analogs, but a relatively high toxicity was also observed. It seems **7a** and **7b** are the most active ones of the compounds synthesized in this study; their anti-writhing activity is worth further investigation.

Most of CNS-acting drugs have a cyclic basic anilide ring as the common molecular structural units.[12] III analogs, which also had similar structural features, might be expected to possess CNS-activities, but the activities of III on the CNS were not so significant according to the observation of general behavioral change.

Changes in the alkyl group represented by $R_1$ produce no marked effect on anti-writhing potency. With respect to 1-(N-substituted amino)alkyl group, when the length of alkylene chain represented by $n$ is changed from 2 to 3, a marked influence on the biological activity was not observed, but the anti-writhing activity is diminished, when $n$ is 1. Replacement of the N-substituents represented by $R_2$ and $R_3$ gives no marked structure-activity relationship. IV analogs that were hydrogenated form of III were synthsized for the purpose of reduction of the toxicity, but they retain relatively high toxicity, and possess pharmacological features similar to that of III.

### Experimental[13]

**3-Methyl-3-phenylindolin-2-one (1a)**——To a solution of 3-phenylindolin-2-one 20.4 g (0.1 mole) in 100 ml of dry DMF was added portionwise sodium hydride (50% dispersion in paraffin oil) 4.8 g (0.1 mole) during 15 min at 5—10° with stirring. The mixture was stirred vigorously for 2 hr at 10°, and 2 hr at 30°. A solution of methyl iodide 15.7 g (0.11 mole) in 20 ml of DMF was added dropwise during 30 min at 5—10°, and stirring for 3 hr at 30°. The reaction mixture was poured into ice water, and the resulting oil was extracted with ether; the ethereal extract was washed, dried and concentrated to give a yellow solid. The solid product was recrystallized from MeOH to give 15.6 g (69.8%) of colorless prisms **Ia**, mp 150—152°. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3200 (secondary amide NH), 1705 (secondary amide C=O). NMR ($CDCl_3$, TMS) $\delta$: 1.79 ppm (3H, s, 3-$CH_3$) 6.7—7.4 ppm (9H, m, aromatic H), 9.48 ppm (1H, b, s, secondary amide NH). *Anal.* Calcd. for $C_{15}H_{13}ON$: C, 80.65; H, 5.87; N, 6.27. Found: C, 80.57; H, 5.71; N, 6.46.

12) Thiazesim: 5[2-(dimethylamino)ethyl]-2,3-dihydro-2-phenyl-1,5-benzothiazepin-4(5H)-one. Dibenzepine: 10-[2-(dimethylamino)ethyl]-5,10-dihydro-5-methyl-11H-dibenzo(b,e)(1,4)-diazepin-11-one.

13) Melting points and boiling points were uncorrected. IR spectra were determined on a Hitachi-215 spectrometer and NMR spectra on a Japan Electron Optics Model JNM-PS 100 spectrometer.

The uncrystallized pasty residue obtained from the filtrate was dissolved in $CHCl_3$, and purified by partition chromatography of silicic acid (60—80 mesh) using IPE as solvent. The first fraction was collected and evaporated, and the residue was distilled under reduced pressure. Pale yellow viscous liquid (1,3-dimethyl-3-phenylindolin-2-one, **8a**) were obtained, bp 149—151° (0.4 mmHg), yield 2.6 g (11%). IR $\nu_{max}^{liq.\ film}$ $cm^{-1}$: 1700 (tertiary amide C=O). NMR ($CDCl_3$, TMS) $\delta$: 1.8 ppm (3H, s, 3-$CH_3$), 3.25 ppm (3H, s, 1-$CH_3$), 6.8—7.5 ppm (9H, m, aromatic H). The second fraction gave 1.3 g (5.8%) of **1a**, mp 150—152°.

**1-Methyl-3-phenylindolin-2-one (9)**——N-Methyl mandelanilide 24.1 g (0.1 mole) was added portionwise to a stirred conc. $H_2SO_4$ (200 ml) at 10—15°. The mixture was stirred for 4 hr at room temperature. The brownish clear solution was poured into crashed ice, and then allowed to stand overnight. The solid material precipitated was collected, washed successively with aq. $NaHCO_3$ and $H_2O$, and dried, which, after crystallization from MeOH–petroleum benzin, gave 19.9 g (86.9%) of **9** as colorless crystals, mp 117—119°. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 1695 (tertiary amide C=O). NMR ($CDCl_3$, TMS) $\delta$: 3.20 ppm (3H, s, 1-$CH_3$), 4.58 ppm (1H, s, methine at position 3), 6.8—7.4 ppm (9H, m, aromatic H). *Anal.* Calcd. for $C_{15}H_{13}ON$: C, 80.65; H, 5.85; N, 6.27. Found: C, 80.78; H, 5.64; N, 5.98.

**3-Ethyl-3-phenylindolin-2-one (1b)**——3-Phenylindolin-2-one 20.9 g (0.1 mole), sodium hydride (50% dispersion in paraffin oil )4.8 g (0.1 mole) and ethyl iodide 17.2 g (0.11 mole) was treated as described above. After continuation of stirring for 4 hr at 60—70°, the reaction mixture was poured into ice water, and the resulting oil was extracted with ether; the extract was washed, dried and evaporated to give a pale yellow solid. The solid product was recrystallized from MeOH to give 17.7 g (72.1%) of colorless prisms **1b**, mp 164—165°. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3180 (secondary amide NH), 1700 (secondary amide C=O). NMR ($CDCl_3$, TMS) $\delta$: 1.31 ppm (3H, t, $J$=8 cps, $CH_2\underline{CH_3}$), 2.28 ppm (2H, q, $J$=8 cps, $C\underline{H_2}Me$), 6.8—7.3 ppm (9H, m, aromatic H), 9.31 ppm (1H, b, s, secondary amide NH). *Anal.* Calcd. for $C_{16}H_{15}ON$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.81; H, 6.51; N, 6.12. The uncrystd. pasty residue obtained from the filtrate was partitioned by chromatography of silicic acid using IPE as solvent into **1b** 1.2 g (4.9%) and 1,3-diethyl-3-phenylindolin-2-one (**8b**) 3.3 g (12.4%), mp 81—82°, colorless columns from IPE. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 1700 (tertiary amide C=O). NMR ($CDCl_3$, TMS) $\delta$: 0.69 ppm (3H, t, $J$=7.5 cps, 3-$CH_2\underline{CH_3}$), 1.25 ppm (3H, t, $J$=7.5 cps, 1-$CH_2\underline{CH_3}$), 2.60 ppm (2H, q, $J$=7.5 cps, 3-$C\underline{H_2}Me$), 3.60 ppm (2H, q, $J$=7.5 cps, 1-$C\underline{H_2}Me$), 6.6—7.5 ppm (9H, m, aromatic H). *Anal.* Calcd. for $C_{18}H_{19}ON$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.26; H, 7.25; N, 5.29.

**3-Methyl-3-phenyl-1-piperidinomethylindolin-2-one (2)**——A suspension of **1a**, 2.2 g (0.01 mole), paraformaldehyde 1.5 g (0.05 mole), piperidine hydrochloride 1.8 g (0.015 mole) and 2 drops of conc. HCl in 50 ml of EtOH was stirred under reflux for 4 hr. To the reaction mixture was added paraformaldehyde 1.5 g (0.05 mole), then the mixture was refluxed again for 4 hr, and concentrated under diminished pressure. The residue obtained was dissolved in water and washed with ether. The water layer was alkalified with conc. NaOH, then the oil separated was extracted with ether. The ethereal extracts were dried over $K_2CO_3$ and evaporated. Maleic acid (0.9 g) was added to a solution of the residual oil (2.3 g) in MeOH. Addition of EtOAc gave 2.8 g (65.0%) of **2** maleate, mp 152° (foaming) as colorless columns (IPA). *Anal.* Calcd. for $C_{21}H_{24}ON_2 \cdot C_4H_4O_4$: C, 68.70; H, 6.47; N, 6.42. Found: C, 68.61; H, 6.44; N, 6.47.

**3-Alkyl-1-(*w*-chloroalkyl)-3-phenylindolin-2-ones (3a—d)**——To a suspension of **1** (0.1 mole) in 200 ml of dry toluene was added sodium hydride (50% dispersion in paraffin oil) 5.8 g (0.12 mole) portionwise. After the mixture was stirred for 1 hr at room temperature, appropriate *w*-chloroalkyl bromide (0.12 mole) was added. The reaction mixture was stirred and refluxed for 8 hr, diluted with ice water, and extracted with benzene. After being dried, the extracts were concentrated, and the residue was purified by distillation or recrystallization to give **3a—d**.

Physical properties and result of microanalysis are listed in Table I.

**3-Alkyl-1-[*w*(N-alkylamino)alkyl]-3-phenylindolin-2-ones (4a—f)**——A mixture of **3** (0.02 mole) and a large excess of the appropriate amine (40 ml of 30% $MeNH_2$ ethanol solution) was heated in autoclave at 100° for 10 hr, evaporated under reduced pressure, and diluted with water. After extracting with ether, the $H_2O$ solution was made alkaline with 10% NaOH and the separated amine was extracted to give crude product, which was purified by distillation and converted into the salt indicated in Table II.

**3-Alkyl-1-[*w*(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 $Me_2NH$, $Et_2NH$, morpholine or piperidine in 40 ml of EtOH) was treated as described for the preparation of **4**. The crude product was purified by distillation under diminished pressure to give (**5a—d**).

b) A suspension of **1** (0.02 mole) and sodium amide 0.86 g (0.022 mole) in 50 ml of dry xylene was stirred for 40 min at room temperature, and *w*-(N,N-dialkylamino)alkyl chloride (0.025 mole) was added. The mixture was stirred and refluxed for 6 hr, diluted with ice-water and extracted with ether. The ether extracts were extracted with 5% HCl. The acid extracts were made alkaline with conc. NaOH, and the separated oil was extracted with ether. After being dried, the ether extracts were concentrated and the residue was distilled to give **5e—p** which was converted into the salt indicated in Table III.

**3-Alkyl-3-phenylindolines (6a, b)**——a) To a stirred solution of **1** (0.1 mole) in 200 ml of dry benzene was added dropwise a solution of $NaAlH_2(OCH_2CH_2OCH_3)_2$ 69.5 g (64% solution in benzene) in 60 ml of dry benzene at room temperature. After addition was completed, the mixture was stirred and refluxed

for 2 hr, then cooled to 10—15°. 10 ml of acetone was added to decompose the excess of $NaAlH_2(OCH_2CH_2OCH_3)_2$, then 10% NaOH was added. The mixture was extracted with ether and the ethereal extracts were extracted with 5% HCl. The acidic extracts were made alkaline with NaOH and the separated oil was extracted with ether. After being dried, the extracts were concentrated and the residue was distilled to give **6a, b** as colorless oil. 3-Methyl-3-phenylindoline (**6a**) bp 125—131° (0.6 mmHg), colorless liquid (87.7%). IR $\nu_{max}^{liq.\ film}$ $cm^{-1}$: 3370 (NH). NMR ($CDCl_3$, TMS) $\delta$: 1.70 ppm (3H, s, 3-$CH_3$), 3.46 ppm (1H, s, NH, exchangeable for deuterium in $D_2O$), 3.55 ppm (2H, AB-q, $J=8$ cps, $\delta_{AB}=11$ cps, methylene at position 2), 6.4—7.3 ppm (9H, m, aromatic H). *Anal.* Calcd. for $C_{15}H_{15}N$: C, 86.08; H, 7.22; N, 6.69. Found: C, 85.80; H, 7.27; N, 6.64. 3-Ethyl-3-phenylindoline (**6b**) bp 138—140° (0.7 mmHg) colorless liquid (89.3%). IR $\nu_{max}^{liq.\ film}$ $cm^{-1}$: 3390 (NH). NMR ($CDCl_3$, TMS) $\delta$: 0.82 ppm (3H, t, 3-C$\underline{H}_2CH_3$, $J=8$ cps), 2.15 ppm (2H, q, $J=8$ cps, 3-C$\underline{H}_2$Me), 3.55 ppm (1H, s, NH, exchangeable for deuterium in $D_2O$), 3.61 ppm (2H, AB-q, $J=9$ cps, $\delta_{AB}=6$ cps, methylene at position 2), 6.5—7.4 ppm (9H, m, aromatic H). *Anal.* Calcd. for $C_{16}H_{17}N$: C, 86.05; H, 7.67; N, 6.27. Found: C, 86.31; H, 7.90; N, 6.60.

b) To a stirred suspension of $LiAlH_4$ 0.8 g in 100 ml of dry ether, 4.5 g of **1a**, was added portionwise. After the mixture was stirred and refluxed for 8 hr, the excess of $LiAlH_4$ was decomposed with 10% NaOH. The ether layer was separated and worked up as above to give **6a** as colorless viscous liquid, bp 125—126° (0.4 mmHg) 3.1 g (72.1%), whose spectroscopic data were identical with those of the authentic specimen obtained by the procedure a).

**3-Alkyl-1-[*w*(N,N-dialkylamino)alkyl]-3-phenylindolines (7a—p)**——a) A mixture of **6** (0.02 mole), *w*-(N,N-dialkylamino)alkyl chloride (0.03 mole), anhyd. $K_2CO_3$ 7.0 g and 100 mg of KI in DMF (100 ml) was stirred and refluxed for 5 hr, diluted with ice-water and extracted with ether. The ether extracts were dried over anhyd. $K_2CO_3$, and concentrated to give crude product, which was purified by distillation under diminished pressure. **7n—p** were prepared by this procedure.

b) A mixture of **6** (0.02 mole), *w*(N,N-dialkylamino)alkyl chloride (0.03 mole) and sodium amide 1.2 g (0.03 mole) in 50 ml of dry toluene was stirred and refluxed for 3 hr, diluted with ice-water and extracted with ether. The ether extracts were dried and evaporated, and the oily residue was distilled to give pure amine. **7a,g,m** were prepared by this method.

c) 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 3 hr, then 5 ml of acetone was added to decompose the excess of $NaAlH_2(OCH_2CH_2OCH_3)_2$ 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. **7b—f, h—l** were obtained by this procedure.

Physical properties and result of microanalysis are listed in Table IV.

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