Potential Psychoactive Indole Derivatives II: Synthesis of 5-Alkoxyindolines *via* Reduction of 5-Alkoxy-2-indolinones

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Abstract ☐ As part of a continuing program to define further the role of the indole nitrogen in influencing activity of psychoactive compounds, a series of 5-alkoxy-3-alkylamino-1,3-dimethyl-2-indolinones and indolines were prepared for central activity studies. The intermediate substituted 2-indolinones were prepared by C-5 alkylation of 5-hydroxy-1,3-dimethyl-2-indolinone followed by C-3 alkylation with appropriately substituted chloroalkylamines. The substituted 2-indolinones were then reduced to the indoline derivatives with lithium borohydride. IR and NMR spectroscopy were utilized for the structural characterization of the synthesized compounds.

Keyphrases ☐ Indolinones, 5-alkoxy-3-alkylamino-1,3-dimethyl substituted—synthesized as potential psychoactive agents, structure-activity relationships of indole derivatives ☐ Indolines, 5-alkoxy substituted—synthesized as potential psychoactive agents, structure-activity relationships of indole derivatives ☐ Psychoactive agents—synthesis of 5-alkoxyindolines by reduction of 5-alkoxy-2-indolinones

Appropriately substituted indoles have been of interest to the pharmaceutical chemist, especially because of the widespread occurrence of the indole nucleus among both naturally occurring and synthetic psychoactive compounds (1). In particular, those indole derivatives with 3-alkylamino and 4-, 5-, or 6-alkoxy substitutions have been shown to possess central activity, namely antidepressant, depressant, and hallucinogenic (2).

As a result of the large number of indole derivatives that are psychoactive, we became interested in the role of the nitrogen of the indole nucleus in determining both the potency and the spectrum of the psychoactivity of these compounds.

The nitrogen of indoline and of 2-indolinone differs from the nitrogen of indole with respect to electronic character. Hence, the relative psychopharmacological properties of substituted 2-indolinones and indolines should further elucidate the importance of the indole nitrogen in psychoactive compounds.

In a previous work (3), the present authors prepared 3-alkylamino substituted 2-indolinones and indolines for central activity characterization. Since alkoxy

substitution in the 4-, 5-, or 6-position of the indole nucleus often leads to changes in psychopharmacological activity, it was of interest to prepare 5-alkoxy derivatives of selected 3-alkylamino substituted 2-indolinones and indolines for their central activity characterization. Therefore, a series of 5-alkoxy-3-alkylamino-1,3-dimethyl-2-indolinones and indolines were prepared in the hope that their psychoactivity relative to that of the corresponding indole derivatives would shed further light on the role of the indole nitrogen in determining central activity of the indole derivatives.

The 5-hydroxy-3-methyl-2-indolinone intermediates were obtained by a procedure based on the methods of Julian *et al.* (4) and Stolle (5). Dialkyl sulfate in benzene was utilized for C-5 alkylation, and further C-3 alkylation was carried out with metallic sodium and the appropriately substituted chloroalkylamine in ethanol. The resulting 5-alkoxy-3-alkylamino-1,3-dimethyl-2-indolinones (Table I) were reduced with lithium borohydride in tetrahydrofuran to give the substituted indoline derivatives (Table II). The synthetic pathway is shown in Scheme I.

EXPERIMENTAL[1]

Preparation of 5-Hydroxy-1,3-dimethyl-2-indolinone Intermediates—The 5-hydroxy-3-monoalkyl-2-indolinones, starting materials for the synthesis of the 3-methyl-3-alkylamino-2-indolinones and indolines, were prepared according to the procedure of Julian and Pikl (6). The yields were in the range of 80% of theory, and IR and NMR spectrophotometric data confirmed the structural assignments.

Synthesis of 5-Alkoxy-3-alkylamino-1,3-dimethyl-2-indolinones (Table I)—The synthetic procedure was adapted from that outlined by Horning and Rutenberg (7). Compounds IIa–VIIIa were prepared by the procedure described below for 3-(2-aminoethyl)-5-methoxy-1,3-dimethyl-2-indolinone (Compound Ia). Pertinent data for these compounds are summarized in Table I.

IR and NMR spectral data were utilized in the characterization of these compounds. The IR spectra showed absorbances at 1725 (amide carbonyl), 1475 (methyl), and 1610, 1500, and 740 (phenyl) cm.$^{-1}$, while the NMR spectra showed peaks (in CDCl$_3$) at 3.8–4.2 (*O*-methyl or methylene), 6.8–7.5 (aromatic substituent), 3.5–3.8 (*N*-methylene), and 0.8–1.1 (3-methyl or methylene) p.p.m.

3-(2-Aminoethyl)-5-methoxy-1,3-dimethyl-2-indolinone (Compound Ia)—Metallic sodium (2.07 g., 0.09 mole) in ethanol (150 ml.) was mixed with 5-methoxy-1,3-dimethyl-2-indolinone (12.0 g., 0.06 mole) in a three-necked flask equipped with reflux condenser, stirrer, drying tube, and dropping funnel. A solution of 2-chloroethylamine hydrochloride (11.6 g., 0.10 mole) and metallic sodium (2.3 g., 0.10 mole) in ethanol (100 ml.) was added dropwise to the ethanolic substituted 2-indolinone solution. The reaction mixture
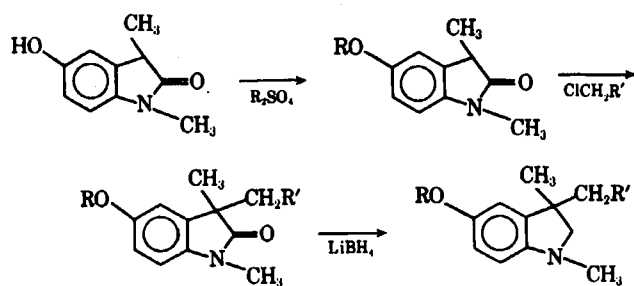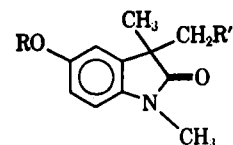

Scheme I

Table I—5-Alkoxy-3-alkylamino-1,3-dimethyl-2-indolinones

Compound	R	R'	Yield, %	Melting Point or Boiling Point (mm. Hg)	Recrystallization Solvent	Formula	Analysis, % Calc.	Found
Ia	—CH₃	—CH₂NH₂	41	137–139°ᵃ	Ether–hexane	—	—	—
IIa	—CH₂CH₃	—CH₂NH₂	38	125–126°	Benzene	C₁₂H₁₈N₂O₂	C 67.74	67.94
							H 8.06	7.96
							N 11.29	11.27
IIIa	—CH₃	—CH₂N(CH₃)₂	32	127–128°ᵇ	Ether	—	—	—
IVa	—CH₂CH₃	—CH₂N(CH₃)₂	39	146–147°	Chloroform–ether	C₁₆H₂₄N₂O₂	C 69.57	69.66
							H 8.70	8.58
							N 10.14	10.10
Va	—CH₃	—CH₂CH₂N(CH₃)₂	34	156–160° (1.2)ᶜ	—	—	—	—
VIa	—CH₂CH₃	—CH₂CH₂N(CH₃)₂	33	121–122°	Ether–hexane	C₁₇H₂₆N₂O₂	C 70.34	70.21
							H 8.97	8.91
							N 9.65	9.73
VIIa	—CH₃	—CH(CH₃)CH₂N(CH₃)₂	25	151–152°	Chloroform–benzene	C₁₇H₂₆N₂O₂	C 70.34	69.92
							H 8.97	8.82
							N 9.65	9.47
VIIIa	—CH₂CH₃	—CH(CH₃)CH₂N(CH₃)₂	40	129–130°	Benzene	C₁₇H₂₆N₂O₂	C 71.01	71.07
							H 9.27	9.20
							N 9.20	9.13

ᵃ Lit. (8) b.p. 210–213° (9.0). ᵇ Lit. (8) b.p. 210–215° (20.0). ᶜ Lit. (8) b.p. 167–170° (1.0).
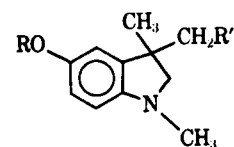
Table II—5-Alkoxy-3-alkylamino-1,3-dimethylindolines

Compound	R	R'	Yield, %	Melting Point or Boiling Point (mm. Hg)	Recrystallization Solvent	Formula	Analysis, % Calc.	Found
Ib	—CH₃	—CH₂NH₂	34	120–122° (1.1)	—	C₁₂H₂₀N₂O	C 70.88	70.82
							H 9.15	9.12
							N 12.71	12.63
IIb	—CH₂CH₃	—CH₂NH₂	28	79–81°	Ether	C₁₄H₂₂N₂O	C 71.75	71.45
							H 9.46	9.45
							N 11.95	11.84
IIIb	—CH₃	—CH₂N(CH₃)₂	37	118–122° (2.0)	—	C₁₅H₂₄N₂O	C 72.53	72.53
							H 9.73	9.59
							N 11.28	11.20
IVb	—CH₂CH₃	—CH₂N(CH₃)₂	32	144–145° (1.3)	—	C₁₆H₂₆N₂O	C 73.28	73.20
							H 10.08	10.11
							N 10.68	10.56
Vb	—CH₃	—CH₂CH₂N(CH₃)₂	38	132–136° (1.4)	—	C₁₆H₂₆N₂O	C 73.28	73.44
							H 10.08	9.85
							N 10.68	10.53
VIb	—CH₂CH₃	—CH₂CH₂N(CH₃)₂	26	77–79°	Ether	C₁₇H₂₈N₂O	C 73.91	73.56
							H 10.14	9.93
							N 10.14	10.04
VIIb	—CH₃	—CH(CH₃)CH₂N(CH₃)₂	33	122–123° (2.4)	—	C₁₇H₂₈N₂O	C 73.91	74.10
							H 10.14	10.02
							N 10.14	9.96
VIIIb	—CH₂CH₃	—CH(CH₃)CH₂N(CH₃)₂	31	82–83°	Methanol	C₁₈H₃₀N₂O	C 74.43	74.62
							H 10.41	10.21
							N 9.64	9.47

was refluxed with stirring for 6 hr. and cooled to room temperature, and then the ethanol was removed under reduced pressure. The resulting brown residue was extracted with ether, and the ether extract was dried over magnesium sulfate. After removal of the ether, the resulting product was recrystallized from ether-hexane to give the compound whose data are summarized in Table I.

Synthesis of 5-Alkoxy-3-alkylamino-1,3-dimethylindolines (Table II)—Reduction of substituted 2-indolinones to indolines was attempted using the procedure outlined by Marion and Kates (8). Since this procedure gave incomplete reduction, the method was altered by utilizing lithium borohydride in tetrahydrofuran. Compounds IIb–VIIIb were prepared by the procedure described for 3-(2-aminoethyl)-5-methoxy-1,3-dimethylindoline (Compound Ib), and their data are summarized in Table II.

The IR spectra of these compounds showed absorbances at 1610, 1500, 740 (phenyl), and 1475 (methyl) cm.⁻¹. The amide carbonyl band was absent. The NMR spectra contained peaks at 6.6–7.2

(aromatic), 3.8–4.2 (O-methyl or methylene), and 3.5–3.8 (N-methylene) p.p.m. with proper multiplicities.

3-(2-Aminoethyl)-5-methoxy-1,3-dimethylindole (Compound Ib)
—A solution of 3-(2-aminoethyl)-5-methoxy-1,3-dimethyl-2-indolinone (5.5 g., 0.03 mole) in tetrahydrofuran (30 ml.) was added slowly to a suspension of lithium borohydride (0.04 mole) in tetrahydrofuran (25 ml.). The reaction mixture was refluxed with stirring overnight and then cooled to room temperature. A mixture of methanol–water (10:1) was added slowly to the mixture until effervescence ceased. The tetrahydrofuran was removed under reduced pressure, and the residue was extracted with ether. The ether extract was dried over magnesium sulfate and the ether evaporated. The crude oil was distilled to give the compound whose data are summarized in Table II.

SUMMARY

Sixteen 5-alkoxy-3-alkylamino-1,3-dimethyl-2-indolinones and indolines were prepared. These compounds were characterized with IR and NMR spectroscopy. Pharmacological testing is in progress.

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Comptonia asplenifolia: Low Boiling Components

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Abstract ☐ Room temperature, low pressure vacuum distillation of 920 g. of the fresh leaves from *Comptonia asplenifolia* Ait. typically yielded 3 mg. of methyl acetate, 1 mg. of ethyl acetate, 2 mg. of diisopropyl acetaldehyde acetal, and 5 mg. of cineol. Methyl acetate, ethyl acetate, and diisopropyl acetaldehyde acetal were not previously reported as components of the essential oil and are important contributors to the odor factors of the plant.

Keyphrases ☐ *Comptonia asplenifolia* Ait.—isolation and identification of low boiling components ☐ GLC—identification of low boiling components of *Comptonia asplenifolia*

Comptonia asplenifolia Ait.[1] was first investigated phytochemically by Braun (1) and later by de Nicola and Lynn (2). Using distillation techniques, these workers isolated 0.02–0.5% by weight of an oil from fresh or semidried leaves. Only cineol was identified. Other compounds such as lactones, terpenes, esters, and alcohols were suggested to be present. In a more recent study using GLC, this essential oil was shown to contain at least 32 identifiable terpenoids including cineol (3). This work utilized a cohobation still, which allowed isolation of high boiling components but precluded observation of volatile compounds and those that were heat or water sensitive. It was, therefore, of interest to isolate such low boiling components. Compounds determined would add to the chemotaxonomic information about *C. asplenifolia*[2].

Using a sequence of room temperature, low pressure vacuum distillation, ether extraction, and temperature-programmed GLC, small amounts of methyl acetate, ethyl acetate, diisopropyl acetaldehyde acetal, and cineol were isolated. The previously undetected methyl acetate and ethyl acetate are common, expected odor contributors. Diisopropyl acetaldehyde acetal, which was isolated in amounts comparable to about half that of the previously noted cineol (2, 3), appears to be another important odor contributor. This is the first report of this substance being isolated from natural

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[1] This plant, a sweet-scented shrub common to the eastern United States, is alternatively designated *Myrica asplenifolia* Endl. or *Comptonia peregrina* L. Coult. and is colloquially named sweet fern. Identification of the plant material used in this study was made by Dr. Fred Barkley of Northeastern University, and a voucher specimen (Clagett and Dubinsky–1) has been deposited with Dr. Barkley, Curator, Husky Herbarium, Northeastern University, Boston, MA 02115

[2] *Comptonia asplenifolia* has been used for many years as a remedy for high blood pressure and as a sickroom air freshener by residents of Appalachia. Its essential oil is patented for use as a perfume fixative (4). The chemotaxonomic information may be useful for chemosystematic evaluations (3).