Synthetic study for 1-methoxyindoles and 1-methoxy-2-oxindoles

SYNTHETIC STUDY FOR 1-METHOXYINDOLES AND 1-METHOXY-2-OXINDOLES[1]

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Abstract ——— The first syntheses of 1-methoxypimprinine, 9-methoxy-β-carboline derivatives, and 3,3-disubstituted 1-methoxy-2-oxindoles are reported. A practical short step synthetic method for 1-methoxyindole-3-acetonitrile is also reported.

Isolation of a number of 1-methoxyindole derivatives[3] from plants and microorganisms prompted us to synthesize 1-methoxy analogs of biologically active indole derivatives. In this report, we wish to describe the first syntheses of 1-methoxypimprinine, 9-methoxy-β-carboline derivatives including 9-methoxyharman, and 3,3-disubstituted 1-methoxy-2-oxindoles. Synthesis of natural auxin,[4] 1-methoxyindole-3-acetonitrile, is also reported.

I. Preparation of 1-Methoxypimprinine

Readily available 1-methoxyindole (2), prepared from 2-nitrotoluene (1) in 62% yield,[5] was reacted with chloroacetyl chloride in refluxing benzene to afford 82% yield of 3-chloroacetyl-1-methoxyindole[6a] (3a). Treatment of 3a with aqueous ammonia in a sealed tube yielded 3-(2-aminoacetyl)-1-methoxyindole[6b] (4) in 35% yield. This compound (4) was found to be unstable and polymerize on standing. Therefore, immediately after preparation of 4 as described above, it reacted without purification with acetyl chloride in methylene chloride and triethylamine to produce 3-(N-acetyl-2-aminoacetyl)-1-methoxyindole[6c] (5) in 44% overall yield. Subsequent treatment of 5 with polyphosphate ester in refluxing chloroform gave 78% yield of 1-methoxypimprinine[6d] (6a). The structure of 6a was confirmed unequivocally by the fact that hydrogenolysis of 5a over 10% palladium on carbon gave 99% yield of pimprinine[7] (6b), which was identical with the sample prepared from 3-chloroacetylindole (3b) according to the same reaction sequences as described above for 6a.

II. Preparation of 1-Methoxyindole-3-acetonitrile

Treatment of 1-methoxyindole (2) with 1-dimethylamino-2-nitroethylene[8] in acetonitrile and trifluoroacetic acid produced 1-methoxy-3-(2-nitrovinyl)indole[6e] (7) in 76% yield. Subsequent reduction of 7 with sodium borohydride in 2-propanol and chloroform in the presence of silica gel[9] afforded 1-methoxy-3-(2-nitroethyl)-indole[6f] (8) in 72% yield. On heating 8 with hexamethylphosphorous triamide[10] and triethylamine in 1,2-dichloroethane at 80°C, it was converted to 1-methoxyindole-3-acetonitrile[6g,11] (9), a natural auxin[4] isolated from Chinese cabbage, in 53% yield. Thus, a practical synthetic method for 9 was established from 2-nitrotoluene (1) in four steps with a 17% overall yield.

III. Preparation of 9-Methoxy-β-carboline Derivatives

Reduction of 7 with lithium aluminum hydride in refluxing ether generated 62% yield of 1-methoxytryptamine[6h,13] (10). Formylation of 10 was carried out by the reaction with formic acid and acetic anhydride at room temperature to yield N_b-formyl-1-methoxytryptamine[6i] (11b) in 91% yield. When the amine (10) reacted with either acetyl chloride or propionyl chloride in methylene chloride and triethylamine, the corresponding N_b-acetyl-[6j] (11c) and N_b-propionyl-1-methoxytriptamine[6k] (11a) were produced in 86% and 81% yields, respectively.

Construction of β-carboline structure was examined under various reaction conditions using 11a, and finally found that synthesis of very unstable 3,4-dihydro-1-ethyl-9-methoxy-β-carboline[6l] (12a) was achieved in 63% yield only when 11a was reacted with phosphoryl chloride at 110°C for 20 min. Subsequent reduction of 12a with sodium borohydride in methanol afforded 1-ethyl-9-methoxy-1,2,3,4-tetrahydro-β-carboline[6m] (13a) in 90% yield, which was stable in contrast to the compound (12a). Similarly, the compounds, (11b) and (11c), were converted to the corresponding 9-methoxy-1,2,3,4-tetrahydro-β-carbolines, (13b)[6n] and (13c),[6o] in 61% and 58% overall yields, respectively by successively conducting of the above mentioned cyclization and reduction.

Oxidation of 12a with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in methylene chloride at room temperature afforded 1-ethyl-9-methoxy-β-carboline[6p] (14a) and 1-ethyl-β-carboline (15) in 4% and 10% yields, respectively. The compound (14a) was quite unstable and decomposed rapidly to 15 on standing. On the other hand, oxidation of 13b with active manganese dioxide[12] (11 mol eq.) in refluxing benzene generated stable 3,4-dihydro-9-methoxy-β-carboline[6q] (12b) in 56% yield. When an excess amount of manganese dioxide (49 mol eq.) was used in refuxing benzene,

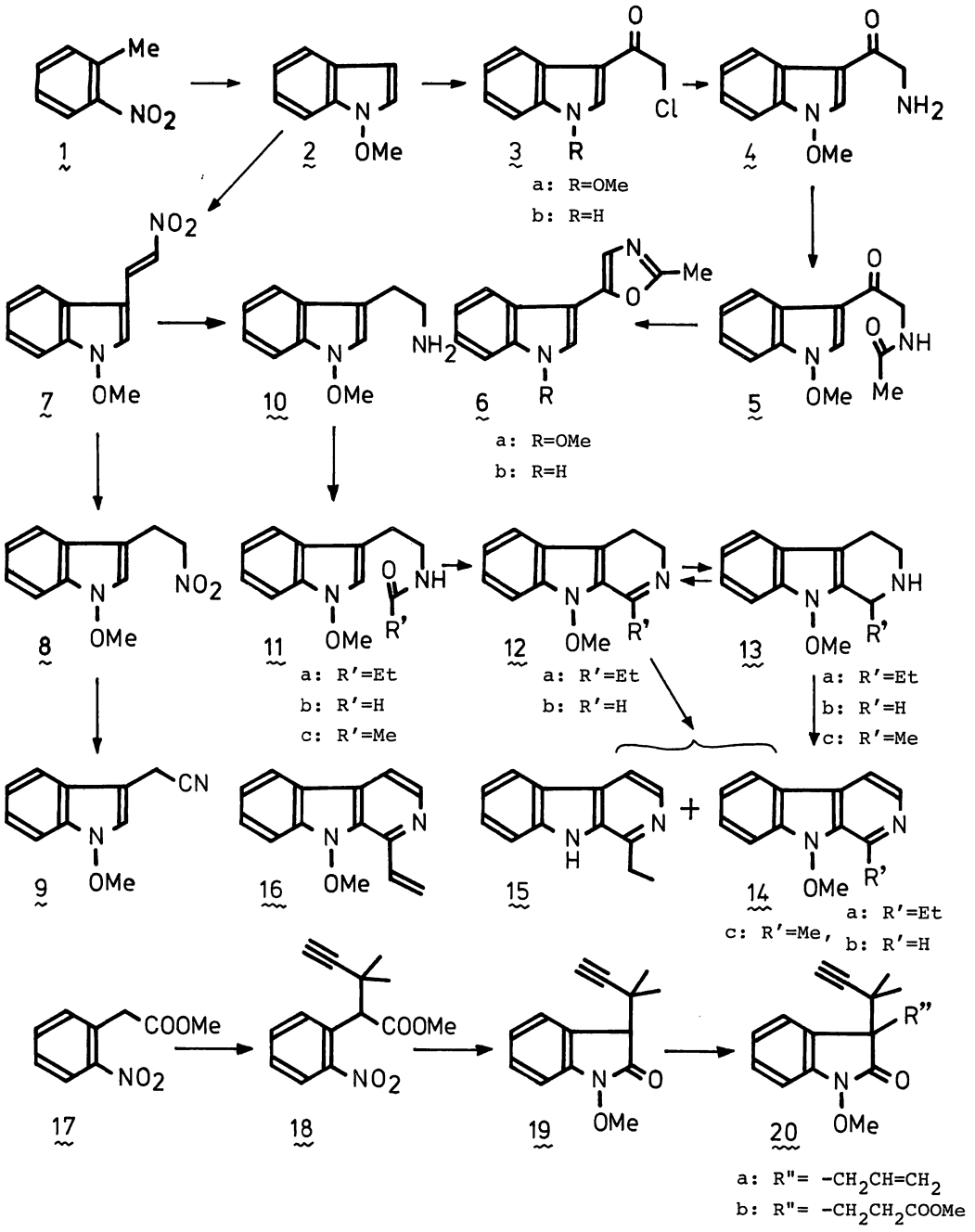
9-methoxy-β-carboline[6r] (14b) was obtained as a stable compound directly from 13b in 50% yield. Under the same reaction conditions, unstable 1-methyl-9-methoxy-β-carboline[6s] (14c), 9-methoxyharman, was prepared in 14% yield directly from 13c. It is interesting to note that there is a significant difference in stability among these compounds (14a-c) and stability order is 14b > 14c > 14a. This result clearly shows that the stability decreases with increasing steric bulkiness of 1-substituent. However, it is not surprising that 9-methoxy-1-vinyl-β-carboline[3b,d] (16) has been isolated as a stable natural product because its 1-substituent has sp^2 hybridized carbons.

Catalytic reduction of 14b over 10% palladium on carbon afforded 86% yield of β-carboline, which was identical with the sample prepared by the conventional method from tryptamine. Thus, the structures of β-carbolines (14a-c) were confirmed.

IV. Preparation of 3,3-Disubstituted 1-Methoxy-2-oxindole Derivatives

The reaction of methyl 2-nitrophenylacetate (17) with 1,1-dimethylpropargyl chloride in the presence of sodium hydride in absolute N,N-dimethylformamide afforded 56% yield of methyl 3-ethynyl-3-methyl-2-(2-nitrophenyl)butylate[6t] (18). Reduction of 18 with zinc and ammonium chloride in methanol and water and subsequent methylation of the resultant 1-hydroxy-compound with ethereal diazomethane produced 67% yield of 3-(1,1-dimethylpropargyl)-1-methoxy-2-oxindole[6u] (19). Treatment of 19 with allyl bromide and potassium t-butoxide in absolute N,N-dimethylformamide generated 69% yield of 3-allyl-3-(1,1-dimethylpropargyl)-1-methoxy-2-oxindole[6v] (20a). Similarly, 3-(1,1-dimethylpropargyl)-1-methoxy-3-(2-methoxycarbonylethyl)-2-oxindole[6w] (20b) was obtained in 83% yield by the reaction of 19 with methyl acrylate and sodium hydride in absolute N,N-dimethylformamide.

In conclusion, 1-methoxyindole structure was found to tolerate to various types of reaction conditions as described above, though demethoxylation was often observed in oxidative reactions and especially under the irradiation of light. Based on these results, we are currently pursuing the synthetic project for oxalines[3a,c,e] and 1-methoxy analogs of ergot alkaloids.


Me
NO2
1
2
OMe
3
R
a: R=OMe
b: R=H
Cl
4
NH2
5
NH
Me
6
Me
7
10
8
11
a: R'=Et
b: R'=H
c: R'=Me
12
13
CN
9
16
15
14
a: R'=Et
c: R'=Me, b: R'=H
COOMe
17
18
19
20
R"
a: R"= -CH2CH=CH2
b: R"= -CH2CH2COOMe

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6. All melting points are uncorrected. All oily compounds gave satisfactory high mass data and crystalline compounds afforded acceptable combustion data. IR absorption bands are shown in cm^{-1}. ^{1}H-NMR signals are reported in ppm (δ) from TMS. a: mp 103.0-104.5°C. IR (KBr): 1661, 1513. ^{1}H-NMR ($CDCl_3$): 4.08 (3H, s), 4.37 (2H, s), 7.31-7.51 (3H, m), 7.84 (1H, s), 8.01-8.34 (1H, m). MS m/e: 225 and 223 (M^+); b: Oil. IR (film): 3346, 1652, 1510. ^{1}H-NMR ($CDCl_3$): 2.21 (2H, br s, NH_2), 3.92 (2H, br s), 4.09 (3H, s), 6.82-7.60 (3H, m), 7.78 (1H, s), 7.99-8.42 (1H, m). MS m/e: 204 (M^+); c: mp 149.0-150.5°C. IR (KBr): 3600-3100 (br), 1656, 1640. ^{1}H-NMR ($CDCl_3$): 2.06 (3H, s), 4.09 (3H, s), 4.53 (2H, d, J=4.4 Hz), 6.63 (1H, br s), 7.00-7.53 (3H, m), 7.90 (1H, s), 8.00-8.33 (1H, m). MS m/e: 246 (M^+); d: mp 49.0-50.5°C. IR (KBr): 1637, 1578. ^{1}H-NMR (CCl_4): 2.42 (3H, s), 4.00 (3H, s), 6.86 (1H, s), 6.78-7.27 (3H, m), 7.31 (1H, s), 7.48-7.75 (1H, m). MS m/e: 228 (M^+); e: mp 99.5-100.0°C (lit.[13] mp 105-106°C). IR (KBr): 1621, 1472, 1308, 1250. ^{1}H-NMR ($CDCl_3$): 4.07 (3H, s), 6.80-7.68 (5H, m), 7.41 and 7.91 (each 1H, d, J=13.0 Hz). MS m/e: 218 (M^+); f: Oil. IR (film): 1548, 1375. ^{1}H-NMR (CCl_4): 3.30 (2H, t, J=7.2 Hz), 3.93 (3H, s), 4.43 (2H, t, J=7.2 Hz), 6.70-7.46 (5H, m). MS m/e: 220 (M^+); g: Spectral data were identical with those of the natural product reported in the literature.[4] Oil. IR (film): 2241. ^{1}H-NMR ($CDCl_3$): 3.71 (2H, s), 4.00 (3H, s), 6.72-7.63 (5H, m). MS m/e: 186 (M^+); h: Oil. IR (film): 3342, 3227, 1614, 1580, 1451, 1320. ^{1}H-NMR (CCl_4): 1.84 (2H, br s, NH_2), 2.49-3.09 (4H, m), 3.87 (3H, s), 6.59-7.42 (5H, m). MS m/e: 190 (M^+); i: Oil. IR (film): 1664, 1532. ^{1}H-NMR (CCl_4): 2.76 (2H, t, J=7.2 Hz), 3.36 (2H, q, J=7.2 Hz), 3.86 (3H, s), 6.39 (1H, br s, NH), 6.62-7.54 (5H, m), 7.71 (1H, br s). MS m/e: 218 (M^+); j: Oil. IR (film): 3261, 1642, 1550. ^{1}H-NMR (CCl_4): 1.74 (3H, s), 2.77 (2H, t, J=6.4 Hz), 3.34 (2H, q, J=6.4 Hz), 3.85 (3H, s), 6.50-7.50 (6H, m). MS m/e: 232 (M^+); k: Oil. IR (film): 1643, 1550. ^{1}H-NMR (CCl_4): 1.01 (3H, t, J=7.0 Hz), 2.01 (2H, q, J=7.0 Hz), 2.77 (2H, t, J=6.5 Hz), 3.35 (2H, br q, J=6.5 Hz), 3.83 (3H, s), 6.58 (1H, br s, NH),

6.73-7.43 (5H, m). MS m/e : 246 (M^+); l: Oil. IR (film): 2934, 1605, 1536. ^{1}H-NMR (CCl_4): 1.19 (3H, t, J=7.0 Hz), 2.63 (2H, t, J=8.0 Hz), 2.73 (2H, q, J=7.0 Hz), 3.70 (2H, t, J=8.0 Hz), 3.84 (3H, s), 6.71-7.44 (4H, m). MS m/e: 228 (M^+); m: Oil. IR (film): 3297, 1452. ^{1}H-NMR (CCl_4): 1.02 (3H, t, J=7.0 Hz), 1.53-2.12 (2H, m), 1.67 (1H, s, NH), 2.42-2.79 (2H, m), 2.86-3.22 (2H, m), 3.70-4.07 (1H, m), 3.84 (3H, s), 6.66-7.36 (4H, m). MS m/e: 230 (M^+); n: Oil. IR (film): 3293, 1456, 1440. ^{1}H-NMR ($CDCl_3$): 1.96 (1H, s, NH), 2.66 (2H, br t, J=6.0 Hz), 3.11 (2H, t, J=6.0 Hz), 3.92 (3H, s), 4.00 (2H, br m), 6.81-7.46 (4H, m). MS m/e: 202 (M^+): o: Oil. IR (film): 3272, 1453. ^{1}H-NMR (CCl_4): 1.36 1H, br s, NH), 1.48 (3H, d, J=6.6 Hz), 2.56 (2H, t, J=6.0 Hz), 3.02 (2H, q, J=6.0 Hz), 3.86 (3H, s), 3.76-4.35 (1H, m), 6.56-7.36 (4H, m). MS m/e: 216 (M^+); p: This compound was quite unstable oil and detected by high resolution mass spectroscopy. Calcd for $C_{14}H_{14}N_2O$: m/e: 226.1105. Found: 226.1108. IR (film): 2930, 1450; q: Oil. IR (film): 1435. ^{1}H-NMR ($CDCl_3$): 2.81 (2H, t, J=8.0 Hz), 3.90 (2H, dt, J=8.0 and 2.5 Hz), 4.04 (3H, s), 6.71-7.61 (4H, m), 8.32 (1H, br s). MS m/e: 200 (M^+); r: Oil. IR (film): 1625, 1451. ^{1}H-NMR ($CDCl_3$): 4.08 (3H, s), 6.94-7.54 (3H, m), 7.70 (1H, dd, J=5.2 and 1.2 Hz), 7.89 (1H, dt, J=7.5 and 1.2 Hz), 8.29 (1H, d, J=5.2 Hz), 8.75 (1H, br s). MS m/e: 198 (M^+); s: Oil. IR (film): 1620, 1569. ^{1}H-NMR (CCl_4): 2.86 (3H, s), 3.94 (3H, s), 6.76-7.40 (3H, m), 7.45 (1H, d, J=4.8 Hz), 7.80 (1H, br d, J=7.2 Hz), 8.08 (1H, d, J=4.8 Hz). MS m/e (212 (M^+); t: mp 82.0-83.0°C. IR (KBr): 2114, 1729, 1528, 1350. ^{1}H-NMR ($CDCl_3$): 1.16 and 1.40 (each 3H, s), 2.20 (1H, s), 3.63 (3H, s), 4.41 (1H, s), 7.08-7.77 (3H, m), 7.89-8.13 (1H, m). MS m/e: 261 (M^+); u: mp 71.0-72.5°C. IR (KBr): 2095, 1706. ^{1}H-NMR ($CDCl_3$): 1.13 and 1.59 (each 3H, s), 2.17 (1H, s), 3.24 (1H, s), 3.87 (3H, s), 6.65-7.32 (3H, m), 7.38-7.67 (1H, m). MS m/e: 229 (M^+); v: mp 44.0-46.0°C. IR (KBr): 2100, 1712. ^{1}H-NMR (CCl_4): 0.95 and 1.54 (each 3H, s), 2.19 (1H, s), 2.81 (2H, d, J=5.8 Hz), 3.83 (3H, s), 4.50-5.15 (3H, m), 6.57-7.33 (3H, m), 7.33-7.70 (1H, m). MS m/e: 269 (M^+); w: Oil. IR (film): 2102, 1737, 1721. ^{1}H-NMR ($CDCl_3$): 1.04 and 1.52 (each 3H, s), 1.66-2.06 (2H, m), 2.27 (1H, s), 2.36-2.76 (2H, m), 3.47 (3H, s), 3.93 (3H, s), 6.72-7.63 (4H, m). MS m/e: 315 (M^+).

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