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TOTAL SYNTHESES OF INDOLE ALKALOIDS, ANNONIDINE A AND 7-(3-METHYL-2-BUTEN-1-YL)INDOLE[1]

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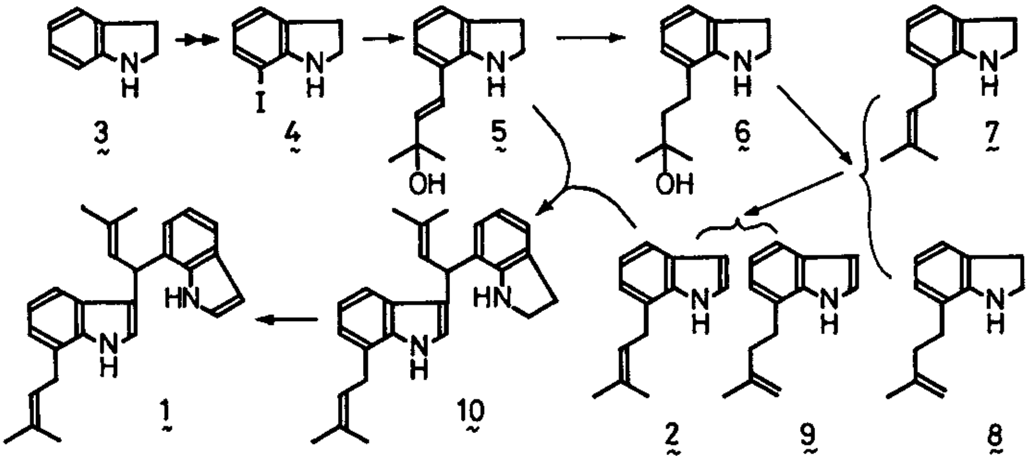
Abstract ——— Practical total syntheses of annonidine A and 7-(3-methyl-2-buten-1-yl)indole are reported.

Achenbach and co-workers[2] isolated annonidine A (1) and 7-(3-methyl-2-buten-1-yl)-indole[3a] (2) from the stem bark of the west african medicinal plant, *Annonidium* Mannii Engl. & Diels (Annonaceae) in 1985. We are much interested in annonidine A because of its hitherto unknown prenylated bisindole structure. In this report, we describe the total syntheses of annonidine A and 7-(3-methyl-2-buten-1-yl)indole.[3b] We have already reported a convenient and practical synthetic method for 2,3-dihydro-7-iodoindole (4) from 2,3-dihydroindole (3) in three steps in 62% overall yield.[4] Heck reaction of 4 with 2-methyl-3-buten-2-ol in the presence of a catalytic amount of palladium acetate in *N*,*N*-dimethylformamide afforded 4-(2,3-dihydroindol-7-yl)-2-methyl-3-buten-2-ol (5, mp 85.0-86.5°C) in 74% yield.[4b] Catalytic hydrogenation of 5 over 10% palladium/carbon at an atmospheric pressure produced 4-(2,3-dihydroindol-7-yl)-2-methyl-3-butanol (6, mp 88-90°C) in 87% yield. Subsequent treatment of 6 with *p*-toluenesulfonic acid in refluxing benzene afforded 95% yield of an inseparable mixture of 2,3-dihydro-7-(3-methyl-2-buten-1-yl)indole (7) and its double bond isomer (8) in the ratio of 13:1. Oxidation of the mixture with dioxygen in the presence of a catalytic amount of salcomine[5] in methanol at room temperature for 2 h afforded 7-(3-methyl-2-buten-1-yl)indole [2, mp 43.5-44.0°C (lit.[2] mp 43-44 °C)] and its double bond isomer (9, mp 18-19°C) in 75% and 3% yields, respectively. Condensation of 2 and 5 in tetrahydrofuran by the action of 2N-hydrochlolic acid produced regiospecifically 3-[1-(2,3-dihydroindol-7-yl)-3-methyl-2-buten-1-yl]-7-(3-methyl-2-buten-1-yl)indole (10, viscose oil) in 78% yield. Subsequent salcomine[5] catalyzed oxidation with dioxygen afforded 3-[1-(indol-7-yl)-3-methyl-2-buten-1-yl]-

7-(3-methyl-2-buten-1-yl)indole [1, mp 105-108°C (lit.[2] mp 106-108°C)] in 65% yield. Spectral data of 1 and 2 were identical with those of the natural alkaloids. Since the present method is simple and practical, synthesis of various derivatives and evaluations of their pharmacological activities are currently in progress.



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REFERENCES AND NOTES

1. This report is part XLI of a series entitled "The Chemistry of Indoles." Part XL: M. Somei, F. Yamada, and K. Naka, Chem. Pharm. Bull., 35, 1322 (1987).
2. H. Achenbach and C. Renner, Heterocycles, 23, 2075 (1985); H. Achenbach and D. Franke, Arch. Pharm. (Weinheim), 320, 91 (1987).
3. a) V. Benesova, Z. Samek, V. Herout, and F. Sorm, Collect. Czech. Chem. Commun., 34, 1807 (1969). b) The first synthesis of 7-(3-methyl-2-buten-1-yl)indole (2) was reported by Natsume and co-workers: H. Muratake and M. Natsume, Heterocycles, 24, 261 (1986). Other related 7-substituted indole syntheses: S. Nakatsuka, T. Masuda, and T. Goto, Tetrahedron Lett., 27, 6245 (1986); M. Akagi and K. Ozaki, Heterocycles, 26, 61 (1985); T. Martin and C.J. Moody, J. Chem. Soc., Chem. Commun., 1985, 1391; A.P. Kozikowski and K. Isobe, ibid., 1978, 1076; S. Inoue, N. Takamatsu, and Y. Kishi, Yakugaku Zasshi, 97, 558 (1977) and see also references cited in the above literatures.
4. a) M. Somei and Y. Saida, Heterocycles, 23, 3113 (1985). b) M. Somei, Y. Saida, T. Funamoto, and T. Ohta, Chem. Pharm. Bull., 35, No. 8 (1987), in press.
5. A. Inada, Y. Nakamura, and Y. Morita, Chem. Lett., 1980, 1287.

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