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THE FIRST TOTAL SYNTHESES OF 9-METHOXYCARBAZOLE-3-CARBOXALDEHYDE AND METHOXYBRASSININ[1] (THE CHEMISTRY OF 1-METHOXYINDOLE)

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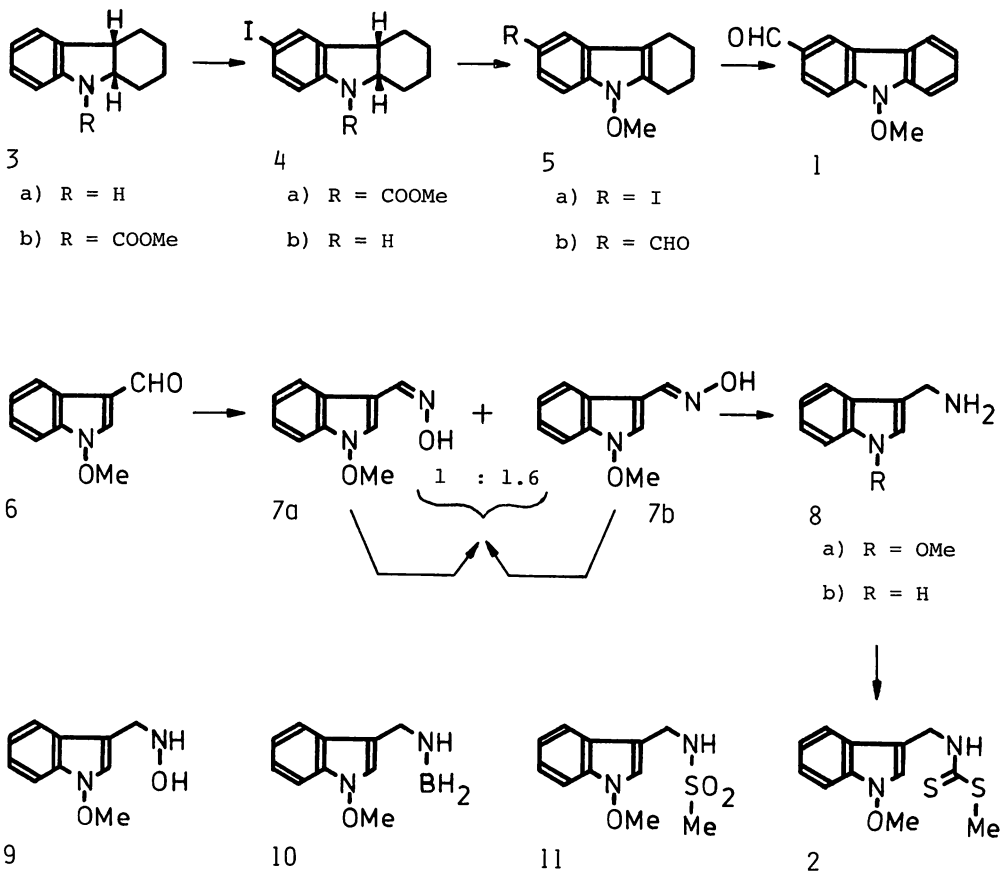
Abstract ——— The first total syntheses of an alkaloid 9-methoxycarbazole-3-carboxaldehyde and a phytoalexin methoxybrassinin are reported.

Recently, alkaloids and glucosinolates having 1-methoxyindole nucleus have attracted much attention because of their biological activities such as phytoalexins[2] or the precursors of anticarcinogenic factors.[3] In 1988, Furukawa and co-workers[4] isolated an interesting 9-methoxycarbazole alkaloid from Murraya euchrestifolia and determined its structure to be 9-methoxycarbazole-3-carboxaldehyde (1, Scheme 1). In the same year, Takasugi and co-workers[2] isolated methoxybrassinin (2) from Chinese Cabbage Brassica campestris L. ssp. pekinensis and established its structure. In our continuing project for preparing biologically active 1-methoxyindole derivatives,[5] we tried various synthetic routes for 1 and 2 without success because of the intrinsic unstable nature of the N-OMe bond to various reactions and light. Finally, we succeeded in the first total syntheses of 1 and 2 by finding the following routes.

Treatment of 4a,9a-cis-1,2,3,4,4a,9a-hexahydrocarbazole (3a) with methyl chloroformate in methylene chloride and triethylamine produced the corresponding 9-methoxycarbonyl compound (3b, mp 68-69°C) in 89% yield. Subsequent iodination of 3b with iodine and sodium periodate[6] in sulfuric acid, acetic acid, and water afforded 6-iodo compound (4a, oil) in 61% yield. Alkaline hydrolysis of 4a gave 4a,9a-cis-1,2,3,4,4a,9a-hexahydro-6-iodocarbazole (4b, mp 94.5-95.5°C) in 85% yield. Next, our synthetic method[7] for 1-methoxyindoles was applied to 4b in methanol and water using 30% aqueous hydrogen peroxide and sodium tungstate as a catalyst, followed by the methylation with ethereal diazomethane, resulting in the formation of 1,2,3,4-

tetrahydro-6-iodo-9-methoxycarbazole (5a, mp 69.5-70.5°C) in 37% yield. Treatment of 5a with n-BuLi in dry tetrahydrofuran and quenching of the resultant lithium compound with dry N,N-dimethylformamide afforded 1,2,3,4-tetrahydro-9-methoxycarbazole-6-carboxaldehyde (5b, oil) in 50% yield. Dehydrogenation of 5b was achieved by the reaction with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in benzene producing 1 in 29% yield.

Scheme 1



On the other hand, methoxybrassinin (2) was synthesized as follows. Readily available 1-methoxy-3-indolecarboxaldehyde[5d,h] (6) led to the corresponding oximes (7a, b) in 98% yield by the reaction with hydroxylamine hydrochloride in pyridine. The tentatively assigned syn- (7a, mp 98.5-99.5°C) and anti-isomer (7b, mp 146-147°C)

were isolated in 59% and 39% yields, respectively, through silica gel column chromatography. Each isomer showed its own ^{1}H-nmr spectrum in CD_3OD, but in $CDCl_3$ or $CHCl_3$ pure 7a and/or 7b changed to the other isomer and attained an equilibrium fairly rapidly (the ratio of 7a and 7b was 1:1.6). Details of the phenomena will be reported in due course.

Attempts to obtain 3-aminomethyl-1-methoxyindole (8a) from the oximes were met with significant problem of the N-OMe bond fission. Thus, reduction of the oximes with $LiAlH_4$,[5h] Zn(Hg)-HCl, or $NiCl_2$-$NaBH_4$[8] completely lost 1-methoxy group culminating in the formation of 3-aminomethylindole[9] (8b, mp 89-90°C). Although reduction with B_2H_6-THF, $NaBH_3CN$-AcOH, or $ZrCl_4$-$NaBH_4$[10] afforded 3-hydroxyaminomethyl-1-methoxyindole (9, oil), the desired 8a was not produced. Finally, we developed a novel and mild reducing method for converting oximes to amines using sodium borohydride (3 mol eq.) and mesyl chloride (3 mol eq.) in dry tetrahydrofuran. Employing this method, the oximes (a mixture of 7a and 7b) were converted to 8a in 21% yield together with its borane complex[11] (10, mp 140-141°C (dec.)) and 3-mesylaminomethyl-1-methoxyindole (11, oil) in 12% and 16% yields, respectively. Subsequent treatment of 8a with carbon disulfide in the presence of triethylamine,[2] followed by the reaction with methyl iodide afforded methoxybrassinin (2) in 64% yield.

The spectral data of the synthetic 9-methoxycarbazole (1) and methoxybrassinin (2) were identical with those of the corresponding alkaloid and phytoalexin.

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