A NEW ENTRY TO INDOLO[2,1-*a*]ISOQUINOLINE SKELETON

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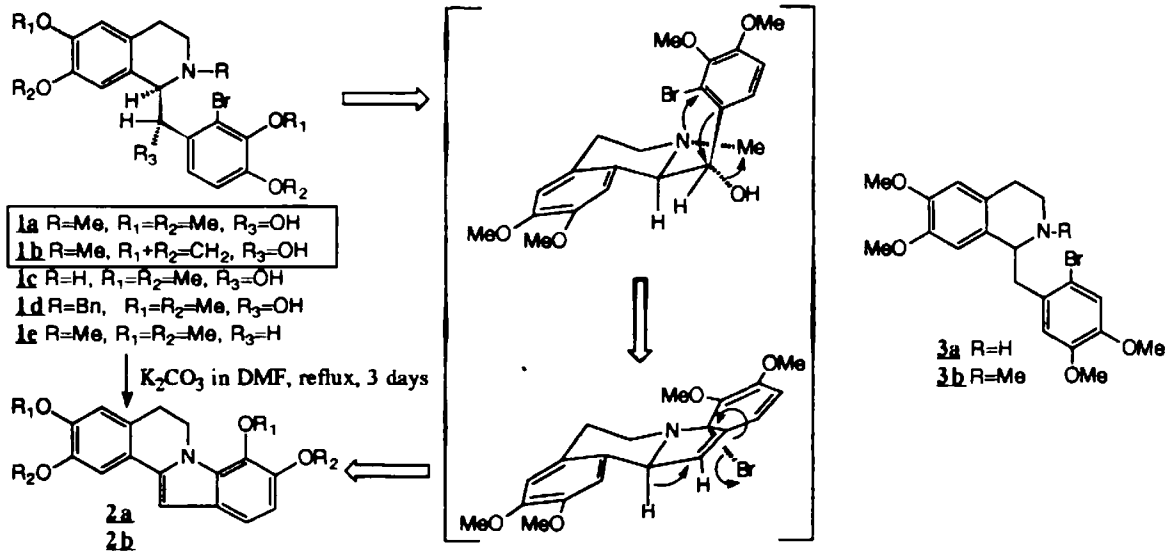
Abstract: *erythro*-1-(β-Hydroxy-2-bromo-3,4-dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline **1a** was almost quantitatively converted to 2,3,8,9-tetramethoxy-5,6-dihydroindolo[2,1-*a*]isoquinoline **2a** by heating with potassium carbonate in N,N-dimethylformamide. This one pot cyclization provides a new entry to the construction of indolo[2,1-*a*]isoquinoline skeleton characteristic of alkaloids, such as cryptaustoline and cryptowoline, isolated from Cryptocaria bowiei.

Indolo[2,1-*a*]isoquinolines have a structural feature of alkaloids, such as cryptaustoline and cryptowoline, isolated from the bark of Cryptocarya bowiei (1). Syntheses of these unique tetracyclic compounds have been accomplished by several methods, such as a benzyne reaction (2) of 1-(2-bromo-4,5-dialkoxybenzyl)-isoquinbolines 3. oxidative coupling of 1-benzylisoquinolines (3), and enamine photocyclization (4), which have been known to give either 9,10-dialkoxyindolo[2,1-*a*]isoquinolines or a mixture of 9,10- and 10,11-dialkoxy-substituted derivatives. Our present method is able to produce 8,9-dialkoxyindoloisoquinolines selectively.

In connection with our synthetic study of heterocyclic compounds involving aromatic metallation, *erythro*-1-(β-hydroxy-2-bromo-3,4-dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline **1a** was treated with palladium diacetate, triphenyl phosphine and excess potassium carbonate in boiling DMF in an atmosphere of carbon monoxide for 3 days (5). However, the expected carbonylation leading to the formation of a phthalide ring did not occur at all, and instead, a new compound **2a** having no N-methyl group was obtained. After careful examinations to clarify the reaction pathway, it was found that this reaction took place smoothly without CO gas, $Pd(OAc)_2$ and PPh_3. On the basis of the ^1H and ^{13}C NMR analysis in comparison with reported spectral data (2f), the structure of this exclusive product 2a was determined to be 2,3,8,9-tetramethoxy-5,6-dihydroindolo[2,1-*a*]isoquinoline 2a. This was also supported by measuring the Nuclear Overhauser Effect as follows. Irradiation of the signal of the proton at position 12 (δ 6.67) resulted in an enhancement of the signal areas of 1-H (20%, δ 7.18) and 11-H (10%, δ 7.24). Irradiation of the doublet signal of the proton at position 10 (δ 6.81) resulted in an enhancement of the signal areas of the aforementioned 11-H (19%) and the methoxy protons (14%, δ 3.95) at position 9.

Methylenedioxy derivative **1b** (6) was also transformed to indoloisoquinoline **2b** under the conditions described above in a good yield. Both N-H **1c** (6) and N-benzyl **1d** (5) derivatives remained unchanged. This reaction requires a fairly high nucleophilicity of the nitrogen atom but not a bulky N-substituent. Isoquinoline **1e**, having no hydroxy group at its benzyl position, was unreactive. Isoquinoline **3a**,b, having no alkoxyl group, at the 3' position was also unreactive, while the benzyne reaction converted them to 9,10-dialkoxyindoloisoquinolines (2a, d). In the preliminary experiments, when a mixture of 2a and its *threo* isomer (5) were subjected to the present cyclization, the *threo* isomer seemed to remain unchanged, although a small amount of the *threo* may have been consumed in the production of **2a** through isomerization to the *erythro* **1a** (7). Thus,

we assumed that the reaction may proceed by an initial attack of the nitrogen atom with the release of steric compression between the Br atom and the neighboring groups, *via* the efficient removal of both hydroxy and N-methyl groups, for instance, along a pathway such as the one shown in the figure. This method provides a new route to the indolo[2,1-*a*]isoquinoline system.



Selected spectral data: 2a: m.p. 193-195°C. IR (Nujol) 1609, 1575, 1556, 1508 cm^{-1}; ^1H NMR (270 MHz) δ 3.09, 4.63 (each 2H, t, J = 6.6 Hz, 5-H_2 and 6-H_2), 3.92, 3.93, 3.95, 3.97 (each 3H, s, 8-,2-,9-,3-OCH_3), 6.67 (1H, s, 12-H), 6.75 (1H, s, 4-H), 6.81, 7.24 (each 1H, AB type, J = 8.6 Hz, 10-H and 11-H), 7.18 (1H, s, 1-H); ^{13}C NMR (270 MHz) δ 29.3 (C-5), 42.1 (C-6), 56.0, 56.0, 57.4, 61.5 (4 OMe), 95.5 (C-12), 107.1 (C-1), 108.3 (C-10), 111.1 (C-4), 115.4 (C-11), 121.6 (C-11a), 125.0 (C-12b), 126.0 (C-4a), 130.1 (C-12a), 135.6 (C-7a), 136.3 (C-8), 148.0, 148.2, 148.6 (C-2, 3 and 9); EI-MS m/z (rel. int.) 339 (M^+, 100), 324 [$(M-CH_3)^+$, 68.7), 170 (23.5); FD-MS 340 [$(M+1)^+$, 24.1], 339 (M^+, 100). 2b: m.p. 205-206°C (EtOH). IR (Nujol) 1598, 1562, 1544, 1502 cm^{-1}; ^1H NMR (270 MHz) δ 3.08, 4.37 (each 2H, t, J = 6.6 Hz, 5-H_2 and 6-H_2), 5.97, 5.99 (each 2H, s, 2 OCH_2O), 6.64 (1H, s, 12-H), 6.72 (1H, s, 1-H), 6.75, 7.06 (each 1H, AB type J = 8.3 Hz, 10-H and 11-H), 7.16 (1H, s, 1-H); ^{13}C NMR (270 MHz) δ 29.5 (C-5), 42.3 (C-6), 96.5 (C-12), 100.7 (OCH_2O), 101.0 (OCH_2O), 103.2 (C-1), 104.4 (C-10), 108.6 (C-4), 112.8 (C-11), 122.3 (C-11a), 122.6 (12b), 126.1 (C-4a), 126.7 (C-12a), 130.8 (C-7a), 135.9 (C-8), 142.9, 147.0, 147.1 (C-2, 3 and 9); EI-MS m/z (rel. int.) 308 [$(M+1)^+$, 23.2], 307 (M^+, 100), 248 (24.0), 153 (24.6).

REFERENCES AND NOTES

(1) J. Ewing, G. K. Hughes, E. Ritchie and W. C. Taylor, Nature 169, 618 (1952); Aust . J. Chem. 6, 78 (1953)
(2) a) T. Kametani and K. Ogasawara, J. Chem. Soc. (c) 2208 (1967). b) F. Benington and R. D. Morin, J. Org. Chem. 32, 1050 (1967). c) T. Kametani, S. Shibuya and S. Kano, J. Chem. Soc. Perkin I 1212 (1973). d) I. Ahmad and M. Gibson, Can. J. Chem. 53, 3660 (1975). e) S. V. Kessar, S. Batra, U. K. Nadir and S. S. Gandhi, Ind. J. Chem. 13, 1109 (1975). f) C. P. Mak and A. Brossi, Heterocycles 12, 1413 (1979)
(3) a) R. Robinson and S. Sugasawa, J. Chem. Soc. 798 (1932). b) J. Harley-Mason, J. Chem. Soc. 1465 (1953). c) U. Hess, K. Hiller and R. S. Schroeder, J. Prockt. Chemie 319, 568 (1977)
(4) I. Ninomiya, J. Yasui and T. Kiguchi, Heteroc cles 6, 1855 (1977)
(5) K. Orito, M. Miyazawa and H. Suginome, Synlett 245 (1994)
(6) 1b (m.p. 187-189°C) and 1d (m.p. 153-155°C) were prepared by the method described in ref. 5.
(7) S. Teitel, J. O'Brien and A. Brossi, J. Org. Chem. 37, 1879 (1972), and ref. cited therein

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