A SYNTHESIS OF BENZOCARBAZOLE DERIVATIVES BY THERMOLYSIS

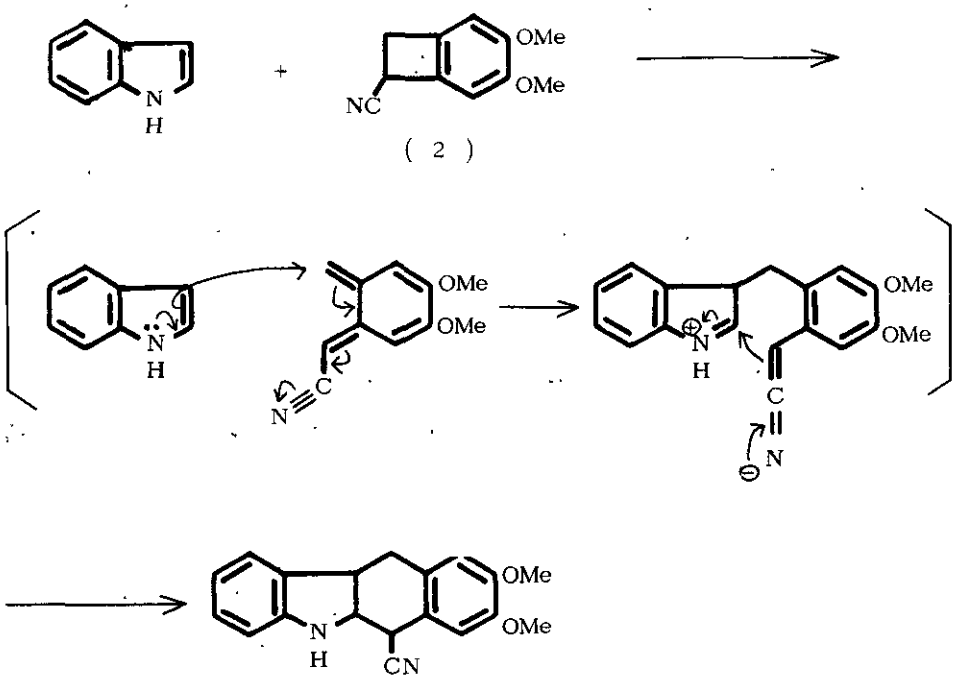
Tetsuji Kametani,* Toshio Suzuki, Kimio Takahashi, and Keiichiro Fukumoto

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai, Japan

A thermal reaction of indolylmagnesium bromide (1) with 1-cyano-4,5-dimethoxybenzocyclobutene (2) gave a mixture of 6-cyano-5a,6,11,11a-tetrahydro-8,9-dimethoxy-5H-benzo[b]-carbazole (3a) and 6-cyano-5a,6,11,11a-tetrahydro-9-hydroxy-8-methoxy-5H-benzo[b]carbazole (4). Compound (3a) was easily converted to 6-cyano-8,9-dimethoxy-5H-benzo[b]-carbazole (6) by dehydrogenation on 30 % Pd-C.

Since Finkelstein,[1] Cava,[2] and Arnold[3] described a benzocyclobutene derivative which underwent many interesting reactions, we also examined this derivative and described in several reports[4,5] the syntheses of isoquinoline alkaloids. As an extension of this method, we now wish to report an intermolecular cycloaddition of indolylmagnesium bromide (1) to 1-cyano-4,5-dimethoxybenzocyclobutene (2).

If the indole reacts with 2 by the following pathway, we could get a cycloaddition product.



(2)

Therefore, at first, a reaction of indole with 2 in refluxing dichlorobenzene was tried, but this afforded only 5,6-dicyano-2,3,8,9-tetramethoxydibenzo[a,e]-cyclooctene (5);[6] subsequently, indolylmagnesium bromide (1) instead of indole was used to enhance the nucleophilicity of indole.

A fusion of 1 and 2 in dichlorobenzene at 160° for 10 min gave a mixture of 6-cyano-5,6,11,11a-tetrahydro-8,9-dimethoxy-5H-benzo[b]carbazole (3a), mp 169 - 170° [$\nu_{max}^{CHCl_3}$ 3430 (NH) and 2250 cm^{-1} (CN)] as a major product in 83 % yield and 6-cyano-5a,6,11,11a-tetrahydro-9-hydroxy-8-methoxy-5H-benzo[b]carbazole (4) [$\nu_{max}^{CHCl_3}$ 3550 (OH) and 2250 cm^{-1} (CN)] in 5 % yield, both of which were easily separated by chromatography on silica gel. The former reaction mixture,

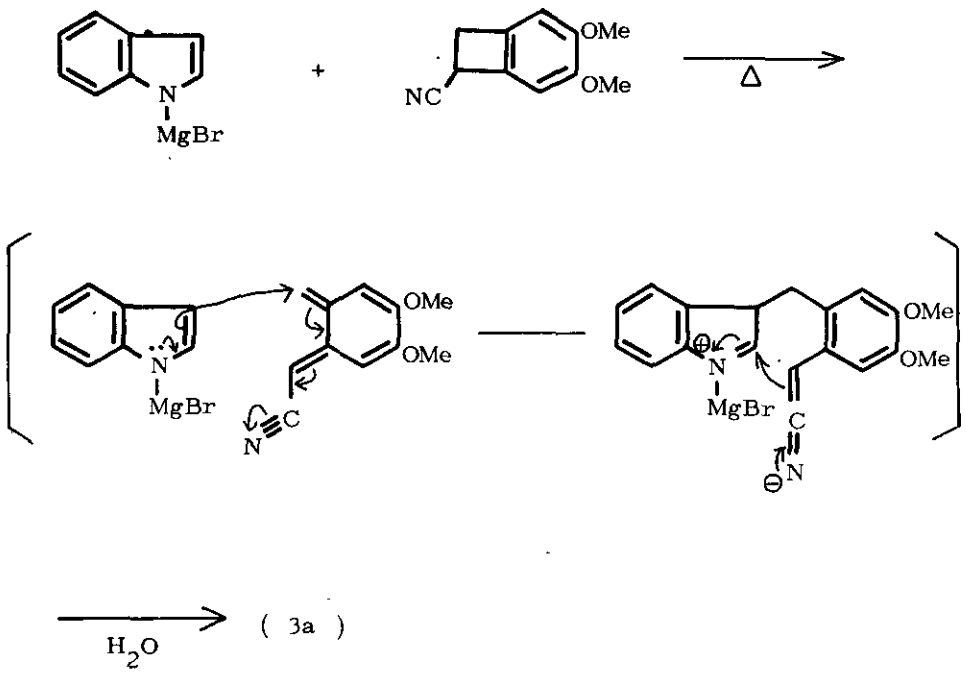
without purification, was treated with an excess of diazomethane, followed by dehydrogenation on 30 % Pd-C in refluxing xylene for 2 h to afford 6-cyano-8,9-dimethoxy-5H-benzo[b]carbazole (5), mp 290° [$\nu_{max}^{CHCl_3}$ 3460 (NH) and 2210 cm^{-1} (CN); m/e 302 (M^+); δ ($CDCl_3$ + DMSO-d_6) 4.02 (3H, s, OCH_3), 4.08 (3H, s, OCH_3), 7.20 - 8.80 (8H, including NH in indole ring and seven aromatic protons consisting of three sharp singlets and unresolved multiplet], in 60 % yield.

The structure of 3a was confirmed by mass and nmr spectroscopy [m/e 306 (M^+), 189, 146 and 117; δ ($CDCl_3$) 2.96 (2H, d, J 5.4 Hz, C_{11} - H_2), 3.0 - 3.2 (1H, broad s, NH, exchange with D_2O), 3.80 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 4.08 (1H, t, d, J 5.4 and 4.6 Hz, C_{11a} - H), 4.74 (1H, d, d, J 10.8 and 4.6 Hz, C_{5a} - H), 6.59 (1H, s, C_{10} - H), 7.00 (1H, s, C_7 - H). 6.38 - 7.12 (4H, m, aromatic protons)]. The proton at C_6-position was obscured by two methoxy resonances. It was also characterized not only by the spectral data of acetylation product (7) [$\nu_{max}^{CHCl_3}$ 2230 (CN) and 1642 cm^{-1} (C=O); δ ($CDCl_3$) 2.52 (3H, s, $COCH_3$), 6.84 (1H, s, C_{10} - H)] but by conversion to compound (6) by direct dehydrogenation of 3a.

The structure (4) was also confirmed by the spectral data of acetylation product (8) [$\nu_{max}^{CHCl_3}$ 2250 (CN), 1760 and 1650 cm^{-1} (C=O); m/e 376 (M^+); δ ($CDCl_3$) 2.32 and 2.54 (each 3H, s, $COCH_3$), 6.95 and 7.0 (each 1H, s, C_7 - H and C_{10} - H).

The position of the hydroxy group of 4 was determined by the fact that the chemical shift of C_{10}-proton in 8 resonates further downfield than that of 4.

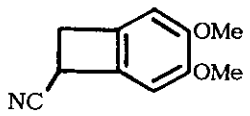
The other possible structure (3b) from this reaction was ruled out not only by the fact that the methylene protons did not couple with the benzylic methine proton but with the lowest methine proton assigned to C_{5a}-H, but also by considering the following reaction mechanism.



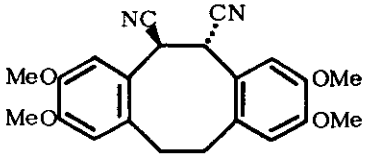
The *configuration of* 3a was *determined* to be cis by the coupling constants described above.

It is supposed that this reaction would proceed via a two step cycloaddition for the following reasons: these types of reactions are always more effective with localized *systems* and they are regioselective.[4,5,6]

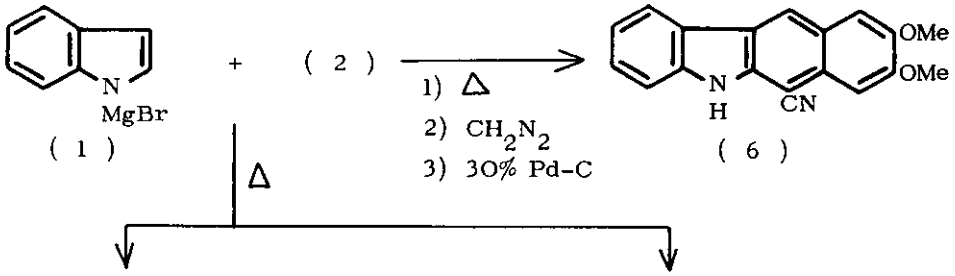
Since the structure of 6 is closely related to olivacine (9) and ellipticine (10), the *indole* alkaloids having an antitumor activity,[7] the synthesis of these types of alkaloids by this method is under investigation.



(2)



(5)



(1)

(6)

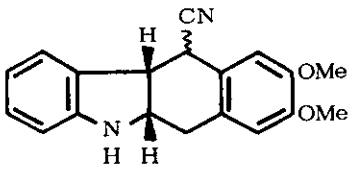
1) Δ
2) CH_2N_2
3) 30% Pd-C

(3a) R^1=H

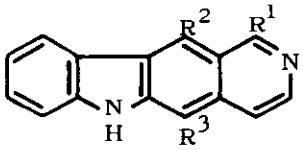
(7) R^1=Ac

(4) R^1=R^2=H

(8) R^1=R^2=Ac



(3b)



(9) R^1=Me, R^2=H, R^3=Me

(10) R^1=H, R^2=Me, R^3=Me

REFERENCES

1 H. Finkelstein, Ber., 1910, 43, 1528.

2 M. P. Cava and D. P. Napier, J. Amer. Chem. Soc., 1956, 78, 500.

3 B. J. Arnold and P. G. Sammes, Chem. Comm., 1972, 1034.

4 T. Kametani, T. Takahashi, and K. Ogasawara, Tetrahedron Letters, 1972, 4847.

5 T. Kametani, K. Ogasawara, and T. Takahashi, Chem. Comm., 1972, 675; Tetrahedron, 1973, 29, 73.

6 T. Kametani, T. Takahashi, K. Ogasawara, and K. Fukumoto, Tetrahedron, in press.

7 R. H. F. Manske, "The Alkaloids", Academic Press, New York, 1968, Vol. XI, p. 279.

Received, 8th November, 1973