A SHORT SYNTHESIS OF RUTECARPINE AND/OR VASICOLINONE FROM 2-CHLORO-3-(INDOL-3-YL)ETHYLQUINAZOLIN-4(3*H*)-ONE: EVIDENCE FOR THE PARTICIPATION OF THE SPIRO INTERMEDIATE

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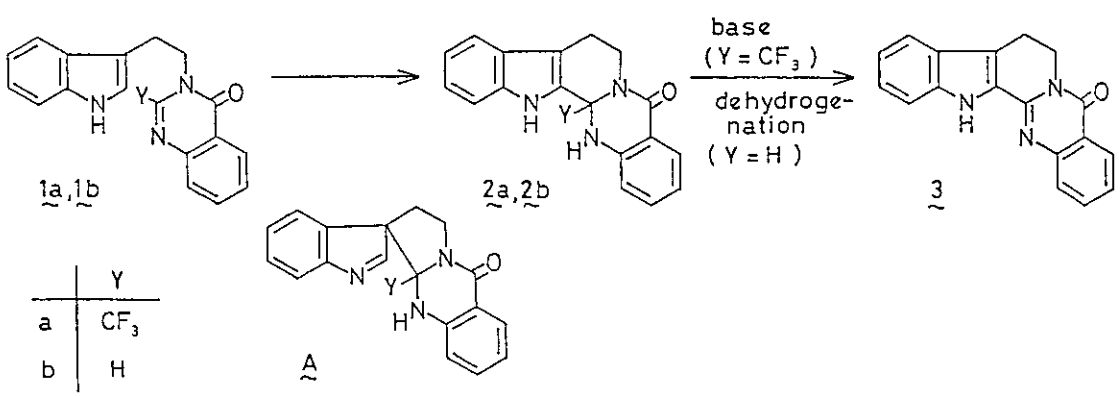
Abstract —— A new route to rutecarpine and/or vasicolinone from 2-chloro-4-quinazolone through an acid catalyzed cyclization of 2-chloro-3-indolylethylquinazolin-4-one has been developed and the mechanism of the cyclization reaction clarified.

Recently, Bergman *et al.* reported a novel synthesis of rutecarpine (3) from 2-trifluoromethyl-3-(indol-3-yl)ethylquinazolin-4-one (1a) *via* an acid-catalyzed cyclization to 2a followed by elimination of CF_3^- by base.[1] The same type of synthesis was reported by Kametani *et al.* who cyclized 3-(indol-3-yl)ethyl-4-quinazolone (1b) by HCl-AcOH to give directly the same alkaloid (3).[2] Obviously, this synthesis includes dehydration of the primary cyclization product (2b) to 3. Bergman's synthesis is superior both in the yield and shortness of the reaction time to that of Kametani *et al.* According to Bergman *et al.*, these superiorities



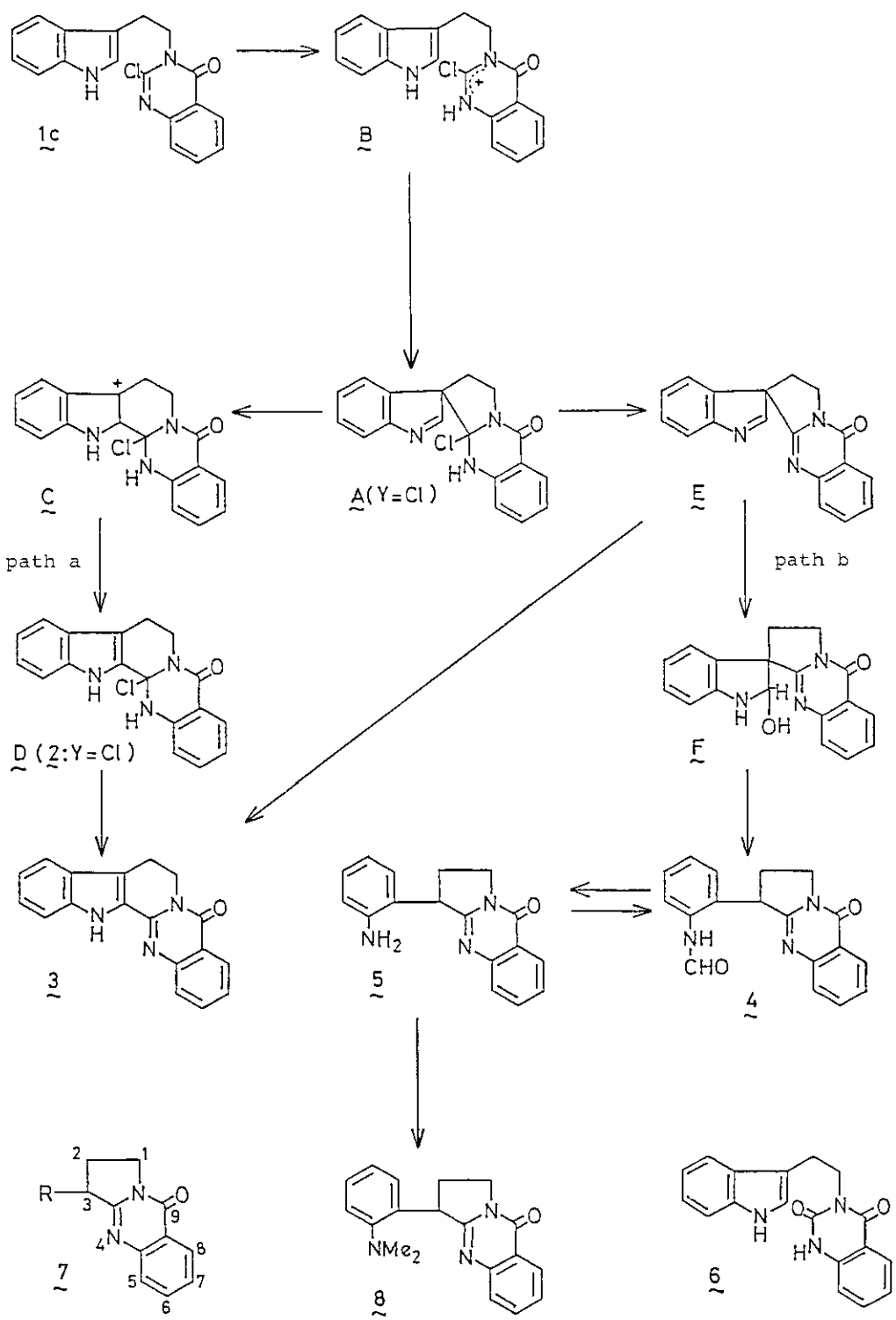
are due to the presence of CF_3 group at the 2-position of the quinazolone ring which not only facilitates the ring closure of 1a to the pentacyclic intermediate (2a) but also acts as a leaving group in the final step (2a → 3).

In these syntheses, however, whether spiro intermediates (A) are involved in the cyclization reaction or not has not yet been determined. Since the importance of the electron-withdrawing CF_3-group is evident in Bergman's synthesis, we have developed an efficient synthetic method of rutecarpine (3), which started from readily available 2-chloro-4-quinazolone.[3] At the same time, we have not only obtained a strong supporting evidence for the participation of a spiro intermediate (A: Y=Cl) in the cyclization step, but also accomplished the synthesis of vasicolinone (8),[4] an alkaloid of *Adhatoda vasica* (Acantaceae).

Reaction of 2-chloro-4-quinazolone with tryptophyl bromide in acetone in the presence of K_2CO_3 (reflux, 20 h) afforded 2-chloro-3-(indol-3-yl)ethylquinazolin-4-one (1c) [mp *ca.* 263°C (dec.);[5] ν_{max} (KBr): 3328 and 1675 cm^{-1}; δ (acetone-d_6); 3.1-3.35 (2H, m), 4.4-4.65 (2H, m), 6.9-7.9 (8H, m), 8.18 (1H, br d, *J* 8 Hz), 10.0 (1H, br s)] and 2-chloro-4-[2-(indol-3-yl)ethoxy]quinazoline [mp 147-148°C; ν_{max} (KBr): 3200 cm^{-1}; δ (acetone-d_6): 3.35 (2H, t, *J* 7 Hz), 4.82 (2H, t, *J* 7 Hz), 6.9-8.0 (8H, m), 8.12 (1H, br d, *J* 8 Hz), 9.95 (1H, br s)] in the respective yields of 68 and 19%. The quinazolone (1c) was then subjected to acid catalyzed cyclization reactions under three different conditions to give three products (3, 4, and 5). The results of these reactions are summarized in Table I.

Table I. Cyclization reactions of 1c under acidic conditions

Run	Reaction condition: Solvent	Time	Temp.	Product (Yield in %): 3	4	5	6
1	$CHCl_3$ containing a small amount of HCl gas	1 h	reflux	44	26	—	—
2	$CHCl_3$ saturated with HCl gas	1 h	room temp.	42	40	—	—
3	conc. HCl-H_2O-MeOH (1:20:180)	17 h	room temp.	9	—	70	20


1c
B
C
A(Y=Cl)
E
path a
path b
D (2:Y=Cl)
F
3
5
4
7
8
6

In Runs 1 and 2, rutecarpine (3) and 3-(2-formamidophenyl)-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-9-one (4) [mp 218-219.5°C; ν_{max} (KBr): 3160, 1660, 1618 cm^{-1}; δ ($CDCl_3$): 2.71 (2H, q, *J* 7 Hz), 4.32 (2H, t, *J* 7 Hz), 4.77 (1H, br t, *J* 7 Hz), 7.0-7.9 (7H, m), 8.13 (1H, br d, *J* 7.6 Hz), 8.35 and 8.5 (1H, each br s 1:3), 10.1 (1H, br s); λ_{max}^{MeOH} nm (log ε): 203 (4.64), 225.5 (4.48), 266 (3.87), 273 (sh)(3.85), 302.5 (3.56), 313.5 (3.48)] were obtained in comparable amounts. In Run 3, however, 3-(2-aminophenyl)-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-9-one (5) [mp 82-84°C; ν_{max} (KBr): 3360, 1662, 1615 cm^{-1}; δ ($CDCl_3$): 2.58 (2H, q, *J* 7 Hz), 4.0 (2H, br s), 4.24 (2H, t, *J* 7 Hz), 4.57 (1H, t, *J* 7 Hz), 6.45-7.7 (7H, m), 8.12 (1H, br d, *J* 8 Hz); λ_{max}^{MeOH} nm (log ε): 203.5 (4.76), 225 (4.53), 229.5 (sh)(4.52), 271.5 (3.93), 291 (3.77), 302 (3.78), 313.5 (sh)(3.61)] was obtained as the major product in 70% yield, together with small amounts of 3 and the hydrolysis product (6) [mp 276-277.5°C; ν_{max} (KBr): 3370, 1700, 1642 cm^{-1}; δ (DMSO-d_6): 2.75-3.2 (2H, m), 3.9-4.35 (2H, m), 6.8-8.1 (9H, m), 10.75 (1H, br s), 11.35 (1H, br s)] in the respective yields of 9 and 20%.

The presence of a set of signals at 4.2-4.3 (2H, t), 2.5-2.7 (2H, q), and 4.5-4.8 (1H, t), and the doublet at the lowest field (8.0-8.2) characteristic to the C_8-proton in a 4-quinazolone moiety revealed the existence of common deoxyvasicinone structure (7) having an aryl function at the 3-position in 4 and 5.[6] These two 3-arylated deoxyvasicinones (4 and 5) were interrelated each other as follows. Thus, treatment of the formyl derivative (4) by HCl/MeOH at room temperature afforded the aniline derivative (5), while refluxing of the latter in formic acid gave the former (4). The yields of both reactions are almost quantitative. Considering the facile hydrolysis of 4 to 5 in HCl/MeOH, it is evident that 4 is formed as the primary product in these reactions and survives only under the conditions of Runs 1 and 2, while in Run 3 compound 4 is solvolyzed to 5. From these experiments, it is obvious that cyclization of 1c proceeds in two different manners, one (path a) giving rutecarpine (3) and the other (path b) the deoxyvasicinone derivatives (4 and 5).

The following mechanism seems to be reasonable which involves the spiro compound (A: Y=Cl) as the common intermediate in these cyclization reactions.

The aza-stabilized carbonium ion (B)[7] formed by protonation of 1c cyclizes to the

spiro compound (A). If no other path is possible for A, it is transformed to the more thermodynamically stable D *via* C[8] and finally affords rutecarpine (3) (path a). In our case, however, the other path may also be possible which would give rise to E by elimination of HCl. Though E might be transformed to 3 by an acid catalyst under anhydrous conditions, addition of H_2O to the imine function of E followed by subsequent retro-aldol type C-C bond fission then affords the vasicinone (4) (path b). In accordance with this explanation, a preferential formation of the vasicinone derivative (5) is only observed in Run 3 whose conditions facilitate the solvolysis of E.

Complete lack of the formation of vasicinone derivatives from 1a and 1b is explainable, because the corresponding spiro intermediate (A) (in which Cl is replaced with H or CF_3) can not afford E due to a poor leaving ability of the substituent and hence only rutecarpine (3) should be formed.

Finally, treatment of 5 with $NaBH_3CN$ and 37% *aq.* HCHO in CH_3CN at room temperature for 2.5 h[9,10] gave the dimethylated product (8) [mp 155-156°C; ν_{max} ($CHCl_3$): 1665, 1615 cm^{-1}; δ ($CDCl_3$): 2.63 (6H, s), 1.9-2.9 (2H, m), 4.0-4.55 (2H, m), 5.02 (1H, t, *J* 9 Hz), 7.05-7.7 (7H, m), 8.26 (1H, br d, *J* 8 Hz)] in 70% yield, which was identical in all respects with those of vasicolinone, an alkaloid of *Adhatoda vasica* (Acantaceae).[4] Hence, we have not only developed a new synthetic method of rutecarpine (3) and/or vasicolinone (8), but also demonstrated an involvement of a spiro intermediate (A) in this sort of cyclization reactions.

ACKNOWLEDGEMENTS

Authors thank Prof. K. Fukumoto, Pharm. Inst., Tohoku University for a gift of an authentic sample of rutecarpine and Dr. H. Miki, Takeda Chemical Industries, Ltd. for 2-chloro-4-quinazolone. This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan.

REFERENCES AND NOTES

1. J. Bergman and S. Bergman, *Heterocycles*, 1981, 16, 347.
2. (a) T. Kametani, C. Van Loc, T. Higa, M. Koizumi, M. Ihara, and K. Fukumoto, *J. Am. Chem. Soc.*, 1977, 99, 2306; (b) T. Kametani, T. Ohsawa, M. Ihara, and K. Fukumoto, *Chem. Pharm. Bull.*, 1978, 26, 1922.
3. H. Miki, *Chem. Pharm. Bull.*, 1982, 30, 3121.
4. S. Johne, D. Gröger, and M. Hesse, *Helv. Chim. Acta*, 1971, 54, 826.
5. Softening at about 135 °C.
6. (a) R. R. Arndt, S. H. Eggers, and A. Jordaan, *Tetrahedron*, 1967, 23, 3521; (b) T. Onaka, *Tetrahedron Lett.*, 1971, 4387.
7. A similar aza-stabilized carbonium ion is suggested in the cyclization reaction of 1a to 2a. See, reference 1.
8. Electrophilic substitution at the 2-position of a 3-substituted indole was demonstrated to occur by an indirect process involving prior attack at the 3-position followed by rearrangement. See (a) A. H. Jackson, B. Naidoo, and P. Smith, *Tetrahedron*, 1968, 24, 6119; (b) E. Wenkert, K. G. Dave, C. T. Gnewuch, and P. W. Sprague, *J. Am. Chem. Soc.*, 1968, 90, 5251.
9. R. F. Borch and A. I. Hassid, *J. Org. Chem.*, 1972, 37, 1673.
10. During the reaction, glacial acetic acid was added occasionally to maintain the pH neutrality.

Received, 1st March, 1985