Communications to the Editor

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A NOVEL THREE-CARBON ANNELATION METHOD FOR PYRIDINE DERIVATIVES[1)]

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Cyclopentane ring annelation methods for 2-pyridone derivatives are provided by cyclobutane ring expansion of 1,2-dihydrocyclobuta[c]pyridin-3(4H)-ones having an appropriate function at the 1-position. Since the latter compounds are readily accessible from 4-alkoxy-2-pyridones via our two-step procedure (Kaneko-Naito method), the methods seem to have wide applicability for the synthesis of cyclopenta[c]pyridines.

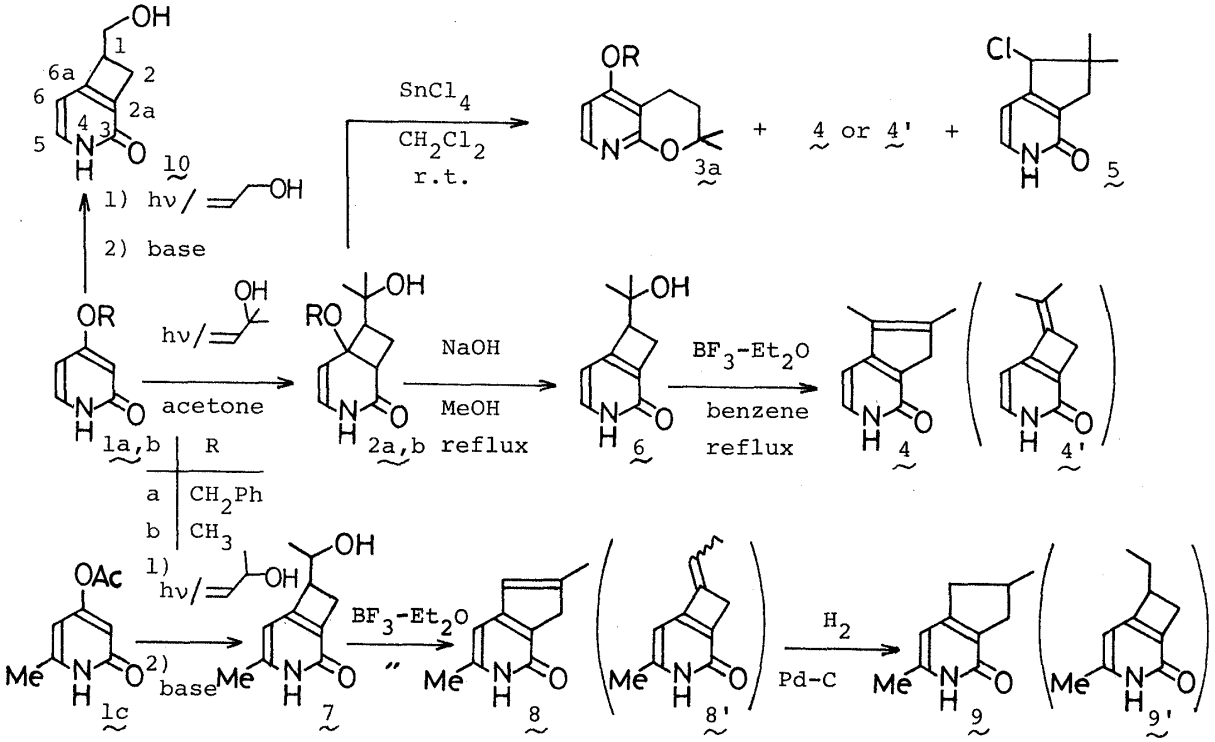
KEYWORDS —— cyclopenta[c]pyridine; cyclopenta[c]quinoline; annelation, cyclopentane ring; ring expansion, cyclobutane

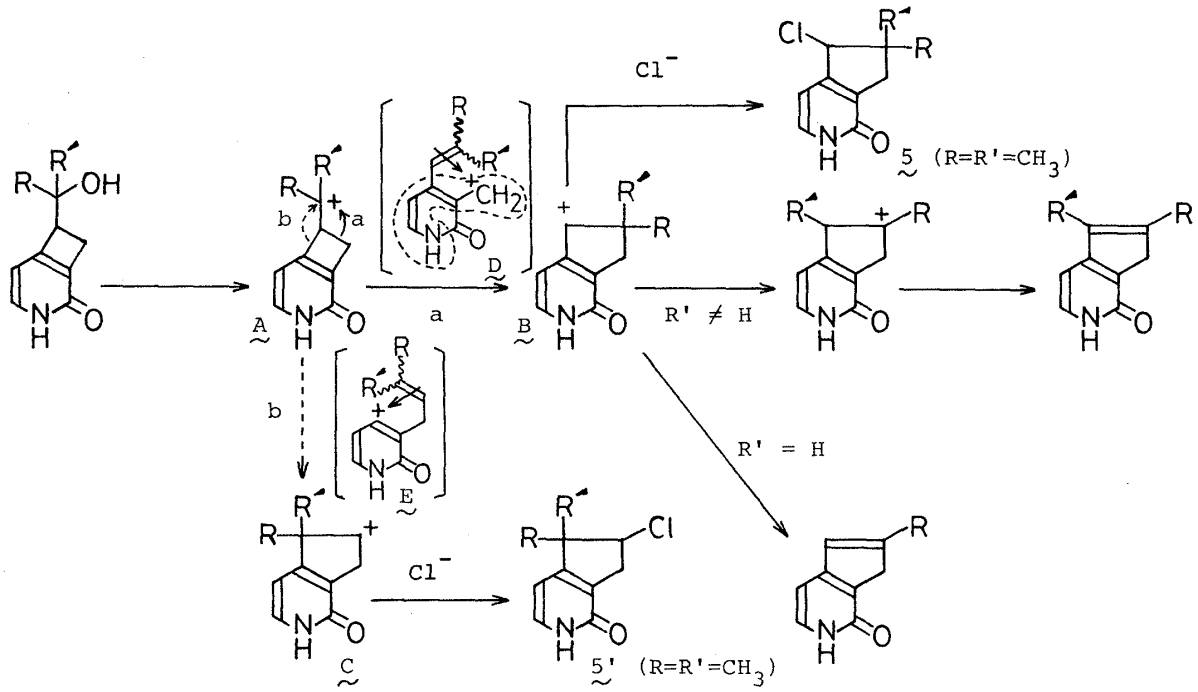
Relief of a considerable strain which is present in cyclobutane derivatives has been known to give cyclopentane derivatives by the fission of one of the cyclobutane σ-bonds.[2,3)] Generally, this expansion is initiated by cationic character at an adjacent carbon to a cyclobutane skeleton. However, such ring expansions are rare for the corresponding cyclobutene derivatives. Thus, benzocyclobutenes readily afford o-quinodimethanes by the C_1-C_2 bond fission upon heating, and the reaction of the latter with olefins affords a well-documented four-carbon annelation method for benzene derivatives[4)] (so-called benzocyclobutene method). Since cyclobutane-fused heteroaromatics have now become readily accessible by our two-step procedure (Kaneko-Naito method) from heteroaromatics having a β-alkoxy enone function in their ring system,[5)] we have attempted to expand their cyclobutane moiety to cyclopentane ring system. Study along this line has led us to find new routes for preparation of cyclopentane-fused pyridines and quinolines.

Previously, we reported that the adduct (2a) obtained by photochemical addition of 4-benzyloxy-2-pyridone (1a) to 2-methyl-3-buten-2-ol gave three products (3a, 4', and 5) upon treatment with $SnCl_4$ in CH_2Cl_2.[6)] Though the structure of the isoprenylation product (3a) was determined unequivocally, those of the other two products were only tentatively assigned at that time. Especially, the structure of 4' was deduced from NMR spectrum, and hence, an alternative structure (4) expectable from the above-mentioned cyclobutane ring expansion was not excluded rigorously. In order to clarify this ambiguity, two cyclobutane-fused pyridones (6, mp 211.5-213°C and 7,[7)] mp 198-206°C) were synthesized from appropriate 2-pyridones (1b and 1c) by our two-step procedure using 2-methyl-3-buten-2-ol or 3-buten-2-ol. Treatment of these pyridones with BF_3-Et_2O in benzene at reflux afforded the corresponding dehydration products (4 or 4', mp 239-242°C (dec.) and 8 or 8', mp 233-236°C) in 60 and 46% yields, respectively. The preference of 8 to 8' for the structure

of the latter product was indicated by a small coupling constant between methyl and olefinic protons in its NMR spectrum [δ($CDCl_3$): 2.14 d (3H, J=1.6 Hz) and 6.20 q (2H, J=1.6 Hz)] and finally confirmed unequivocally by the appearance of the methyl signal at δ 1.12 as a doublet (J=5.6 Hz) in the spectrum of its dihydro derivative (9, mp 186-187°C) obtained from 8 by catalytic hydrogenation (Pd/C). This fact clearly eliminates the cyclobutene structure (9') for the dihydro derivative. This is because, if 9' is the actual structure, its methyl signal should appear as a triplet. Since the two dehydration products showed almost the same UV spectra (λ_{max}^{MeOH} nm: 4: 230, 279, 310 and 8: 227.5, 269, 320), we have now determined the structures of the dehydration products as 4 and 8. Under these conditions, however, 1-hydroxymethyl derivative[8] (10) was recovered unchanged, and no ring expansion products were obtained.

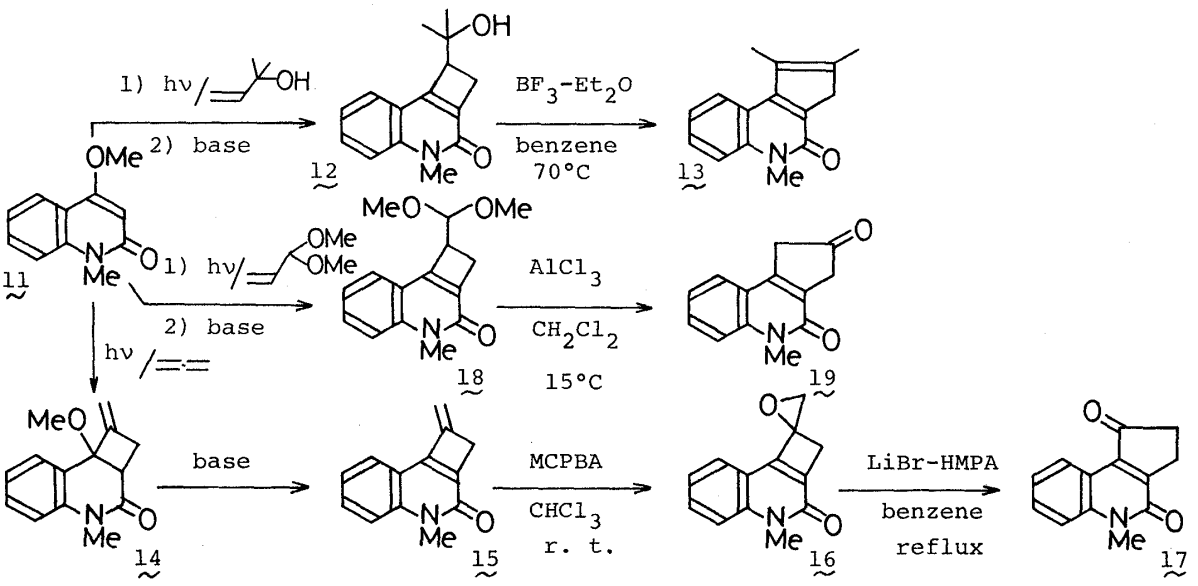
The following mechanism is proposed for this ring expansion reaction. First, a carbonium ion (A) is formed at 1'-position in the 1-substituent. Then a Wagner-Meerwein rearrangement of one (a) of the cyclobutene σ-bonds occurs to give a ring expanded carbonium ion (B), which by deprotonation (directly or after an alkyl migration) affords the final products. The other ring expansion path (b) to give the ion C should not occur as judged from the relative stability of the corresponding transition states (D and E). The π-complex (D) should be more stable than E, because the cationic character of the migration center in D is stabilized by a preferable conjugation as depicted by dotted line.[9,10] The structure of 5 obtained in the previous experiment[6] also fits well with the above mechanism, because if it is formed via path b its structure should be 5'. However, NMR spectrum of 5 clearly indicates that the methine and methylene groups are not directly connected to each other [δ($CDCl_3$): 4.73 s (1H), 2.67 br s (2H)].





The same ring expansion reactions are also found to occur in the corresponding quinolones (e.g., 12⟶13: mp 200-201°C), and hence the method seems to have wide applicability for the annelation of cyclopentane ring to heteroaromatics, insofar as the substituent on the cyclobutene ring has either a secondary or tertiary alcohol in the 1'-position.

Using 1-methylene-1,2-dihydrocyclobuta[c]quinolin-3(4H)-ones[11] which are also readily available from 4-methoxy-2-quinolones and allene by our two-step procedure, another cyclopentane annelation method was disclosed. Thus, the epoxide (16, mp 170-172°C) obtained in 79% yield from 15 by m-chloroperbenzoic acid oxidation was treated with LiBr-HMPA[12] in benzene at reflux to give the cyclopentenone (17, mp 202-203°C, ν_{max}^{KBr} cm^{-1}: 1708) in nearly quantitative yield. The structure of 17 was



determined by NMR spectrum showing the four methylene protons at δ 2.85 as a typical A_2B_2 multiplet. The cyclopentenone isomeric to 17 [19, mp 219-223.5°C (dec.), ν_{max}^{KBr} cm^{-1}: 1750, δ($CDCl_3$): 3.47 s and 3.60 s (each 2H)] was synthesized in 12% yield from 1-dimethoxymethyl cyclobutene[13] (18, mp 103-104°C) by treating the latter with $AlCl_3$ in CH_2Cl_2 at 15°C followed by mild acid hydrolysis. These two reactions thus provide site-selective cyclopentanone annelation for 2-quinolones.

The cyclopentane annelation methods described above not only provide new routes to cyclopentane-fused pyridones and quinolones, but also disclose another type of utilization of the four-membered ring strain in cyclobutane-fused heteroaromatics.[14]

REFERENCES AND NOTES

1) Part XVI of "Cycloadditions in Syntheses." For Part XV, see Reference 11.
2) R. Breslow, in "Molecular Rearrangements," Part 1, P. de Mayo, Ed., Interscience, New York, 1963, p. 278.
3) S.W. Baldwin, in "Organic Photochemistry," Vol.5, A. Padwa, Ed., M. Dekker, New York, 1981, p. 204.
4) For leading references, see: W. Oppolzer, Synthesis, 1978, 793; T. Kametani and K. Fukumoto, Heterocycles, 3, 29 (1975).
5) Synthesis of cyclobutane-fused heteroaromatics and an extension of the benzocyclobutene method to heteroaromatic compounds are reviewed recently. See: C. Kaneko and T. Naito, Heterocycles, 19, 2183 (1982).
6) T. Naito, Y. Momose, and C. Kaneko, Chem. Pharm. Bull., 30, 1531 (1982).
7) A diastereomeric mixture.
8) H. Fujii, K. Shiba, and C. Kaneko, J. Chem. Soc., Chem. Comm., 1980, 537.
9) For a detailed discussion on carbonium ion rearrangements, see: M.J.S. Dewar, in Reference 2, p. 321-323.
10) A migration (b) analogous to phenyl migration via bridged benzenonium ion species would not occur in this case, because the migration center is β-position in the enone system and, hence, electron-deficient.
11) C. Kaneko, N. Shimomura, Y. Momose, and T. Naito, Chem. Lett., in press.
12) Lithium salt catalyzed epoxide-carbonyl rearrangements were originally reported by Rickborn et al.: R. Rickborn and R.M. Gerkin, J. Amer. Chem. Soc., 93, 1693 (1971). See also B.M. Trost and L.H. Latimer, J. Org. Chem., 43, 1031 (1978).
13) Synthesis of this type of compound is readily achieved by our two-step procedure using an acrolein acetal as an olefin in the first photo-addition step. See References 5 and 6.
14) So far, utilization of such ring strain in benzocyclobutenes and their heteroanalogues has been limited to the annelation of six-membered ring (so-called benzocyclobutene method). See References 4 and 5.

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