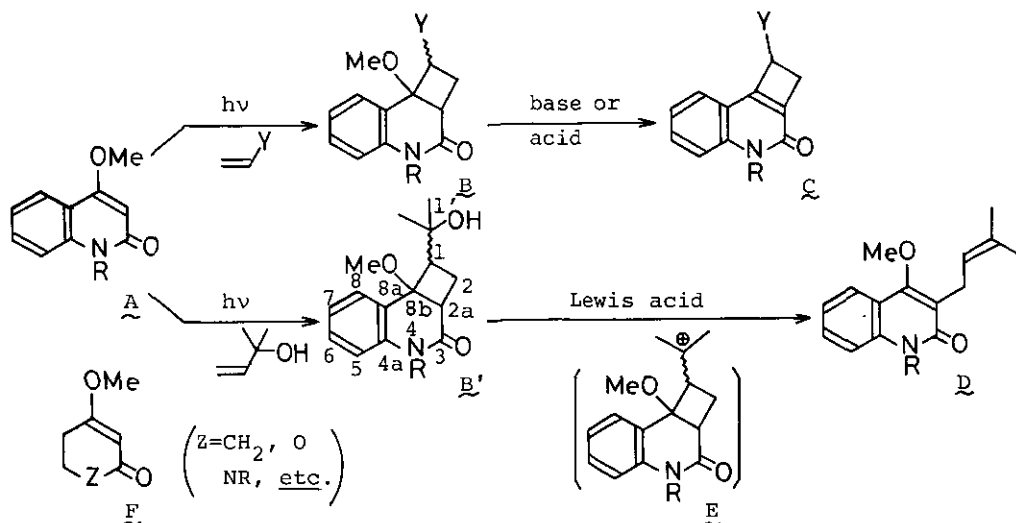


REACTIONS OF 6-METHOXY-3-AZABICYCLO[4.2.0]OCTAN-2-ONE AND ITS 7-SUBSTITUTED DERIVATIVES¹⁾

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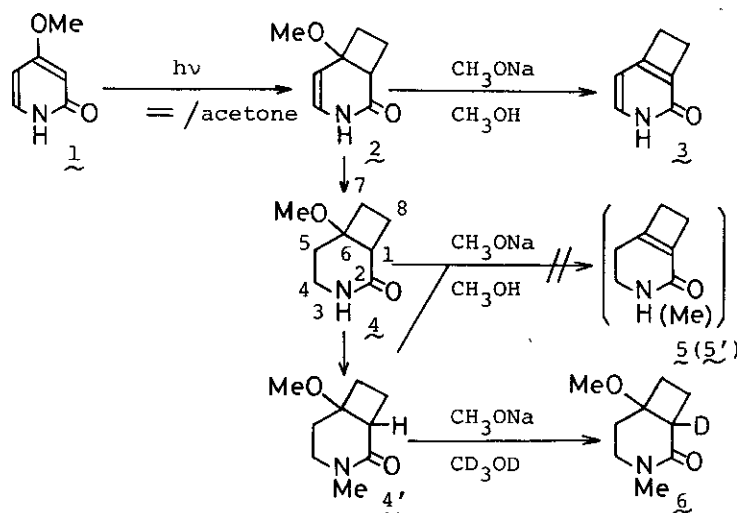
Abstract — The mechanisms of two synthetically useful reactions using photoadducts obtained from 4-methoxy-2-pyridone and a variety of olefins as key intermediates, namely the cyclobutane-annulation and isoprenylation to 2-pyridone, have been clarified using the dihydro derivatives of these adducts (6-methoxy-3-azabicyclo[4.2.0]octan-2-ones) as the starting materials. A possible extension of these two methods to aliphatic enone series is suggested.

In the previous papers of this series, we have disclosed two novel and synthetically useful reactions using photoadducts obtained from 4-methoxy-2-quinolone (A) and a variety of olefins as the key intermediates.^{2,3)} The first reaction corresponds to the second step in the two-step synthetic method (Kaneko-Naito method) of cyclobutane-fused quinolones (C) by the elimination of methanol from the adducts (B).²⁾ The second reaction is isoprenylation and related alkylations of 2-quinolones at the 3-position by the fission of C₁-C_{8b} bond in the adducts (B') initiated by a carbocation formation at the 1'-position in the 1-substituent.³⁾ Though these two reactions have been found to have wide applicability for other heteroaromatic compounds having an appropriate α,β -enone function in their ring



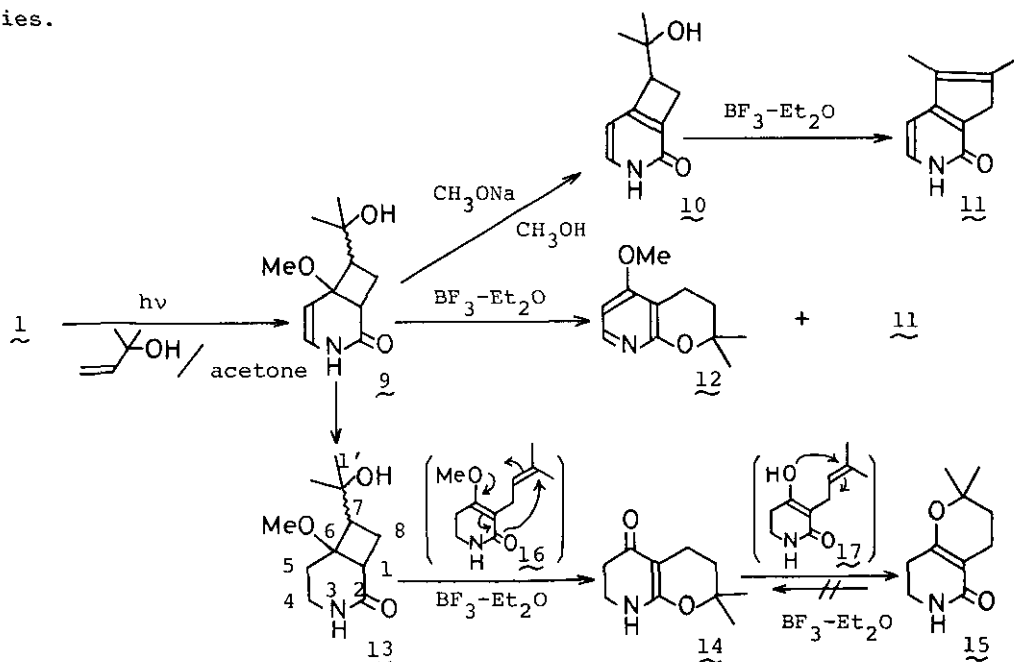
system,⁴⁾ mechanisms for these reactions have remained to be clarified. That is, though the aromaticity due to the pyridone ring is gained in both reactions (c.f., c and d), it is not yet clear whether the gain of aromaticity is an indispensable requisite for each reaction or not. The clarification of the mechanism is important not only for understanding the nature of these reactions but also for extending these reactions to aliphatic enone series (e.g., f).

As the starting materials for the present study, we have chosen 6-methoxy-3-azabicyclo[4.2.0]octan-2-one (4) and its 7-dimethylhydroxymethyl derivative (13). The former (4, mp 89-90°C) was easily prepared in high yield by catalytic hydrogenation (Pd/C) of the adduct⁵⁾ (2) formed by photo-addition of 4-methoxy-2-pyridone (1) to ethylene under acetone-sensitized conditions. Since the adduct (2) was converted smoothly to 1,2-dihydrocyclobuta[c]pyridin-3(4H)-one (3) by refluxing in NaOCH₃/CH₃OH,⁵⁾ 4 was treated under the same conditions. However, the starting material was recovered quantitatively. Complete recovery of the starting material was also observed, when the 3-methyl derivative (4', oil) obtained from 4 in quantitative yield by refluxing the latter in benzene containing NaH and methyl iodide was subjected to the same reaction using CD₃OD instead of CH₃OH. In this case, however, the recovered material was mono-deuterated at the 1-position. The position of deuterium in the product (6) was deduced from NMR spectrum in which a triplet at δ 3.00 (J=10 Hz) which is present in the spectrum of 4' was disappeared. This conclusion is consistent with the mass spectral comparison between 4' and 6. Thus, the base peaks of 4' and 6 appeared at m/z 141 and 142, both of them correspond to the fragment ions caused by elimination of ethylene from the respective molecular ions.⁶⁾ These facts clearly show that the cyclobutane-annulation method developed by us for heteroaromatics (Kaneko-Naito method) is only applicable for compounds, if the final products gain an aromatic system by the methanol-elimination step. Hence, the application of this method to the related aliphatic series (f) should necessarily require to have the better leaving group (e.g., OAc, OTs) at the β -position of the starting enone system.^{7,8)}



Next, we applied the isoprenylation reactions of 2-pyridone derivatives to the corresponding aliphatic series. The starting material (13, mp 149-149.5°C) was prepared by catalytic hydrogenation of previously reported photoadduct (9) obtained from 1 and 2-methyl-3-buten-2-ol.^{3,9)} Upon treatment by $\text{BF}_3\text{-Et}_2\text{O}$ in benzene at reflux, the adduct (9) afforded the isoprenylation product (12) together with some ring-expanded products (e.g., 11).^{3,10)} By treatment with $\text{BF}_3\text{-Et}_2\text{O}$ under the same condition as above, the dihydro derivative (13) afforded two pyranopyridones (14, mp 172.5-173°C and 15, mp 150-151°C) when the reaction was terminated as soon as almost all of 13 was consumed. However, if the reaction was continued further, the former decreased with the increase of the latter, and finally only the latter (15) became the sole product. Though the structures of 14 and 15 could not be distinguished clearly from NMR spectra,¹¹⁾ the following mechanism as well as UV and IR spectra¹²⁾ of the products (14 and 15) suggests strongly the correctness of the assigned structures. Thus, a carbocation is formed at the 1'-position in 13 by the acid-catalysed elimination of hydroxyl group, which by $\text{C}_6\text{-C}_7$ bond fission and deprotonation to give 16 as a primary isoprenylation product. Subsequent acid-catalysed cyclization of 16 then affords a linear pyranopyridone (14). This compound isomerized to the more stable angular pyranopyridone (15) via the ring-opened intermediate (17).

By the above experiments, the mechanisms of the two reactions: Kaneko-Naito method for the synthesis of cyclobutane-fused heteroaromatics and isoprenylation of 2-pyridones and 2-quinolones are clarified. Furthermore, the present study demonstrated not only that Kaneko-Naito method can not be applied to the corresponding aliphatic series so long as the starting materials contain 3-alkoxy-enone function, but also the isoprenylation reaction of heteroaromatics discovered for the first time in 2-quinolone series may be applicable likewise to the aliphatic enone series.

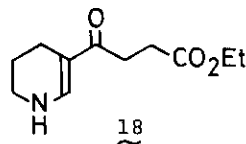


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- 4) Syntheses and reactions of cyclobutane-fused heteroaromatics have been reviewed recently: C. Kaneko and T. Naito, Heterocycles, 19, 2183 (1982).
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- 6) The photo-adducts of this kind as well as their dihydro derivatives show the olefin-eliminated ions as the base peak in their mass spectra.
- 7) It is reported that the bicyclic ketoacetate obtained by photoaddition of ethylene to the enol acetate of cyclohexane-1,3-dione eliminated acetic acid by treatment with K-tert-butoxide in tert-butanol: P.E. Eaton and K. Nyi, J. Amer. Chem. Soc., 93, 2786 (1971).
- 8) An attempted synthesis of 6-acetoxy derivative of 4 from 4-acetoxy-2-pyridone and ethylene has failed, because the elimination of acetic acid from the photo-adduct occurs so readily that 3 was obtained directly after purification of the adduct.
- 9) Though the photoaddition proceeds stereoselectively, the stereochemistry of the adduct (9) is not determined as yet.
- 10) Recently, we have clarified not only the structure of 11 [previously assigned tentatively as 1-dimethylmethylene-1,2-dihydrocyclobuta[c]pyridin-3(4H)-one³] as having an expanded cyclopentane structure, but also its formation occurred through the cyclobutene (10). See, C. Kaneko, T. Naito, Y. Momose, N. Shimomura, T. Ohashi, and M. Somei, Chem. Pharm. Bull., in the press.
- 11) $\delta(\text{CDCl}_3)$ of 14: 1.29 s (6H), 1.67 t, 2.31 t, 2.42 t, 3.42 t (each 2H with J=7.2 Hz), 4.58 bs (1H), and that of 15: 1.27 s (6H), 1.66 t (2H, J=6.2 Hz), 2.0-2.5 m (4H), 3.32 t (2H, J=7.2 Hz), 5.44 bs (1H).
- 12) IR ($\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1570, 1531 for 14 and 1652, 1630 for 15) and UV ($\lambda_{\text{max}}^{\text{MeOH}}$ nm: 298 for 14 and 215, 253 sh for 15) also fit well to the respective structures. The UV maximum (298 nm) of 14 indicates the presence of a N=C=C=O chromophore, since ethyl γ -3-(1,4,5,6-tetrahydropyridyl)- γ -oxobutyrate (18) is reported to show its maximum at 302 nm. Also, a similarity between the IR spectra of 14 and 18 [$\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1731 (ester), 1575, 1512] indicates a significant contribution of the zwitterionic structure ($\text{N}^+=\text{C}=\text{C}=\text{O}^-$) in each compound. For UV and IR spectra of 18, see: P.M. Quan and L.D. Quin, J. Org. Chem., 31, 2487 (1966).



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