HETEROCYCLES, Vol. 6, Nos. 9, 10, 1977

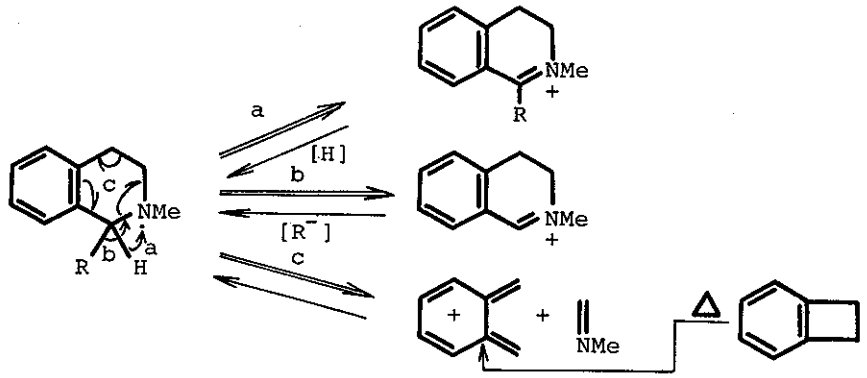
A NEW SYNTHESIS OF QUINAZOLONE ALKALOIDS BY AN INTERMOLECULAR CYCLOADDITION OF IMINOKETENES

Tetsuji Kametani, Keiichiro Fukumoto,* Masataka Ihara, and Chu Van Loc

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

Recently, a systematic method available for the synthesis of complicated compounds has been discussed[1] and Corey has developed a computer-assisted synthetic analysis, which allowed the automatic processing of a target molecular structure in the retrosynthesis.[2] We have also been interested in a development of an effective way for the synthesis of complex molecules[3] and here will discuss our new synthetic approach, which we call Retro Mass Spectral Synthesis,[4] based on the analysis of a fragmentation process in the mass spectrum used widely in a structural determination of organic compounds.

Since fragmentation in mass spectrum is a chemical process that results in bond breaking, fragmentation of a compound in the mass spectrum is sometimes closely similar to chemical degradation reactions. For example, cyclohexene produces butadiene ion radical and ethylene in its fragmentation, a process which is also observed in chemical reaction. On the other hand, cyclohexenes can be obtained from butadienes and ethylene derivatives by a Diels-Alder reaction. These phenomena indicate that some mass spectral fragmentations parallel chemical degradation processes and therefore also parallel retro-processes of synthetic reactions of organic compounds. In fact, typical isoquinoline syntheses correspond to retro-process of the fragmentation patterns in isoquinolines as shown in the following scheme.

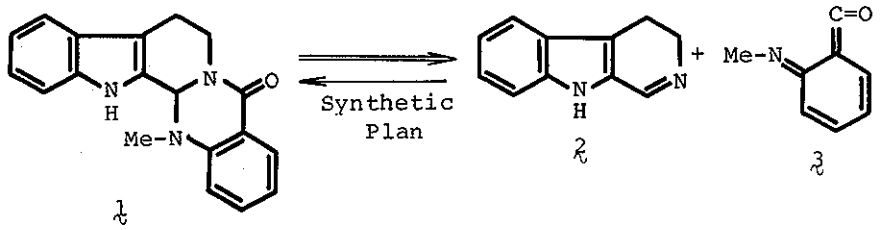


⟹ means mass spectral fragmentation process

⟶ indicates chemical reaction

On this consideration, we examined a total synthesis of the alkaloids having a quinazolone system by retro mass spectral synthesis.

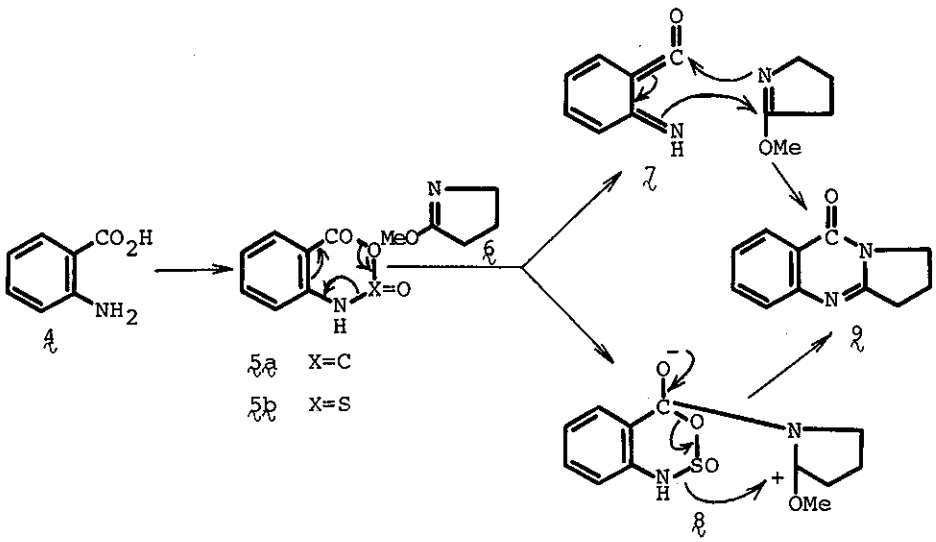
Evodiamine (1), a typical member of the quinazolinocarboline alkaloids, showed two characteristic ions, 2 and 3 by a retro-Diels-Alder reaction of ring D in its mass spectrum. This phenomenon indicates that evodiamine (1) could be synthesized from 3,4-dihydro-β-carboline (2) and the iminoketene 3.



1 2 3

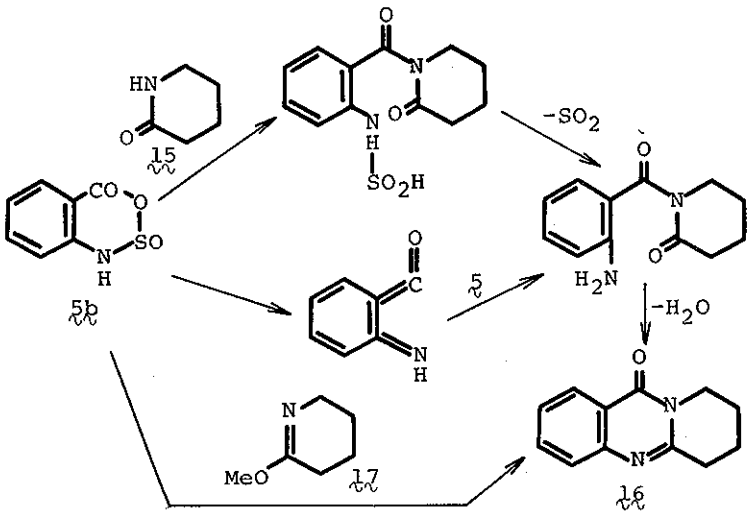
First, we investigated a synthesis of the iminoketene 7, whose reaction with cyclic imines was carried out as a model experiment. It has been well known that the reaction of anthranilic acid (4) hydrochloride with phosgene afforded isatoic anhydride (5a), whose condensation with imines was investigated under severe condition. Since the mechanism had not been reported in the above reaction, we assumed that an intermediate would be iminoketene 7, formed by an

elimination of carbon dioxide by a retrograde Diels-Alder type reaction as shown in the following chart. In our case cycloaddition reaction with imines would be hoped to proceed under mild conditions and, therefore, sulfinamide anhydride 5b was used as a possible precursor of 7.

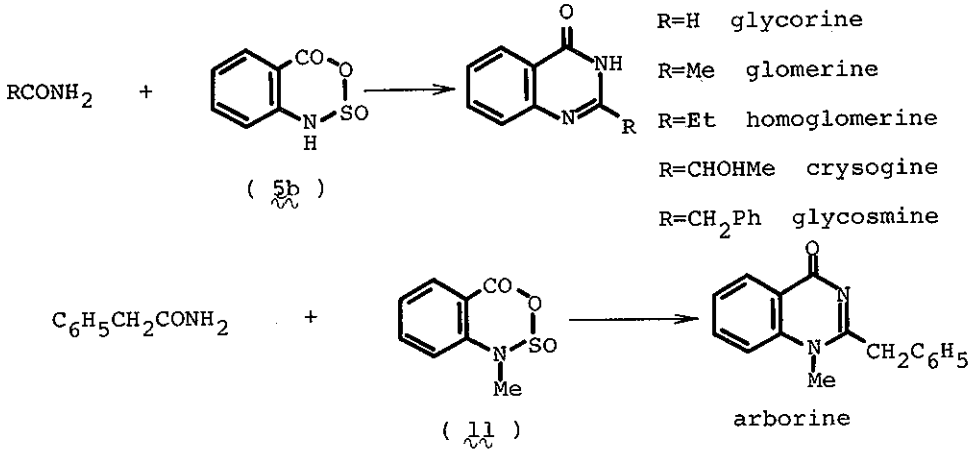


Heating anthranilic acid (4) with thionyl chloride in dry benzene under reflux gave the unstable sulfinamide anhydride 5b. The reaction of 5b with O-methylpyrrolidone (6), which was unstable on heating, was carried out in dry benzene at room temperature for 1-2 h to afford regiospecifically deoxyvasicinone (9) in good yield. In this reaction, the sulfinamide anhydride 5b could have been converted into the iminoketene 7, which would regiospecifically react with 6 by a concerted ($_{\pi}4 + _{\pi}2$)cycloaddition pattern to form deoxyvasicinone (9). However, since the anhydride 5b is prepared by heating at 80° C without decomposition to the iminoketene 7, a stepwise mechanism via the intermediate 8 is likely.[5]

On this finding, a synthesis of evodiamine (1) was investigated by the same reaction as above; thus heating N-methylanthranilic acid (10) with thionyl



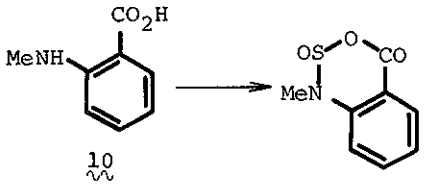
On this finding, several alkaloids were prepared by the reaction of sulfinamide anhydrides with the appropriate amides as shown in the following chart.[6,7]



Rutecarpine (12) was also synthesized from N-formyltryptamine (18) through indolylethylquinazolone derivative (19).[6]

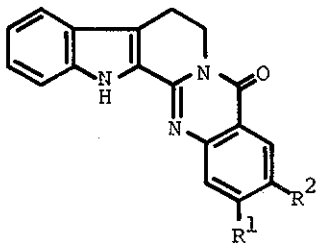
chloride gave an unstable sulfinamide anhydride (11), which was treated with 3,4-dihydro-β-carboline (2) in dry benzene at room temperature to afford regiospecifically evodiamine (1), in 65 % yield along a retro-process of mass spectrum of 1.[5]

By the same method, rutecarpine (12),[5] euxylophoricine A (13)[6] and C (14)[6] were prepared from the corresponding iminoketenes and 2.



10

11

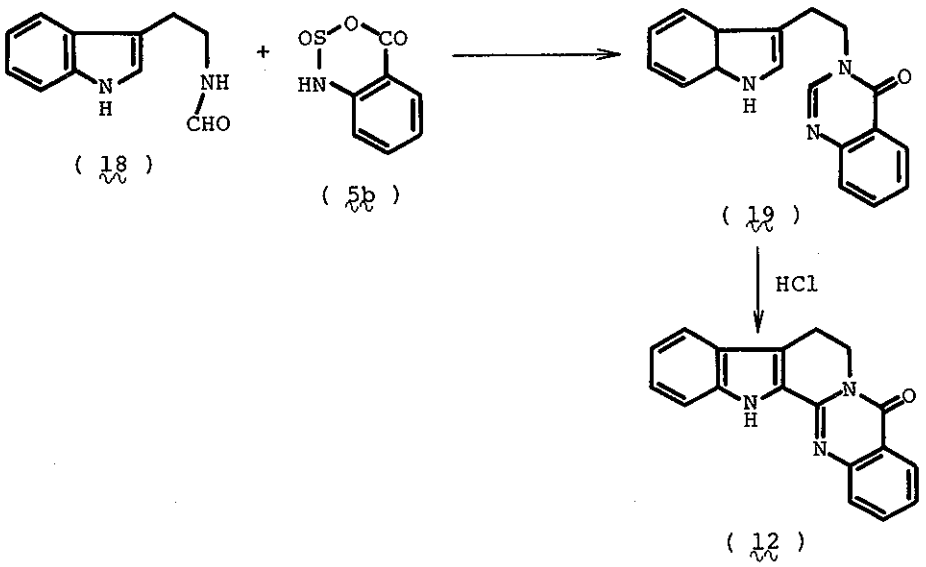


(12) $R^1=R^2=H$

(13) $R^1=R^2=OMe$

(14) $R^1+R^2=OCH_2O$

Secondly, we investigated the reaction of iminoketenes with amides as an extension of our method. Thus, the sulfinamide anhydride 5b, was treated with 2-piperidone (15) in dry benzene at room temperature overnight to give an alkaloid from Mackinlaya species, 6,7,8,9-tetrahydropyrido[2,1-b]quinazolin-11-one (16) in 90 % yield, as shown in the following chart. This structure was proved by direct comparisons with the authentic sample, prepared in 82.4 % yield from the sulfinamide anhydride 5b and O-methylpiperidone (17).



(18) (5b) (19) (12)

References

1. E. J. Corey, Quart. Rev., 1971, 25, 455.

2. E. J. Corey, W. J. Howe, and D. A. Pensak, J. Amer. Chem. Soc., 1974, 96, 7724.

3. T. Kametani and K. Fukumoto, Heterocycles, 1973, 1, 129.

4. T. Kametani and K. Fukumoto, Account Chem. Res., 1976, 9, 313.

5. T. Kametani, T. Higa, C. V. Loc, M. Ihara, M. Koizumi, K. Fukumoto, J. Amer. Chem. Soc., 1976, 98, 6186.

6. T. Kametani, C. V. Loc, T. Higa, M. Ihara, and K. Fukumoto, to be submitted.

7. T. Kametani, C. V. Loc, T. Higa, M. Koizumi, M. Ihara, K. Fukumoto, J. Amer. Chem. Soc., 1977, 99, 2306.