SYNTHESES OF QUINAZOLONE ALKALOIDS AND BENZOXAZINONES BY RETRO MASS SPECTRAL SYNTHESIS AND RELATED ANALYSIS

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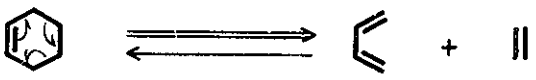
Total synthesis of quinazolone and indoloquinazolone alkaloids by an analysis based on retro mass spcetral synthesis is described. Moreover this account mentions a simple synthesis of quinazolone alkaloids and benzoxazinones by a synthetic procedure developed from retro mass spectral synthesis.

I. INTRODUCTION

There are many natural products isolated from plants and in some cases animals, whose structures have been determined by the systematic use of chemical and spectroscopic methods.[1] Recently, X-ray analysis, especially X-ray analysis connected with a computer system has played an important role in structural determination. In contrast, there is no systematic way for a total synthesis of the complicated natural products, by the result of which their synthesis has depended on the original ideas of the research workers although synthetic organic chemistry has a long history. However, Nature provides a splendid synthetic route

of natural products, which we call biogenesis. In fact, biogenetic-type synthesis[2] is a nice method for a synthesis of complicated natural products, such as morphine and colchicine. Sometimes, photolytic reaction can be applied to a total synthesis of strained or complicated natural products that cannot be obtained by a reaction in the ground state.[3,4] Recently, Corey[5] exploited a computer-assisted synthetic analysis that allows the automatic processing of a target molecule in the antithetic direction.[6]

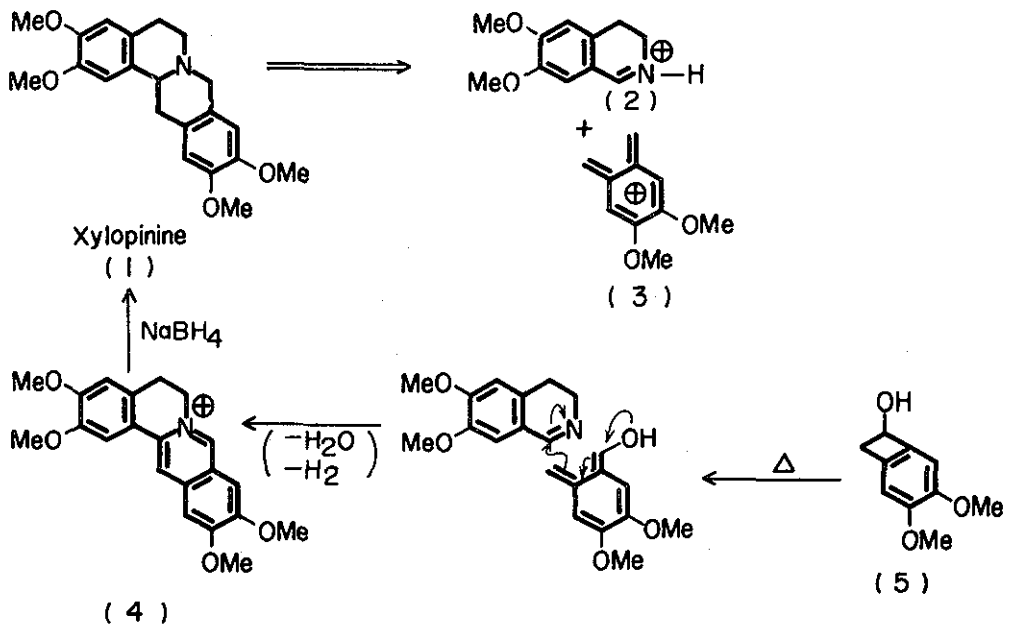
The mass spectrum of an organic compound usually provides a knowledge of the molecular weight or formula, and in some case the molecular structure.[7] Since fragmentation in mass spectrometry is a chemical process that results in bond breaking, a fragmentation is sometimes closely similar to chemical degradation reactions. For example, cyclohexene, which can be obtained from butadienes and ethylene derivatives by a Diels-Alder reaction, produces butadiene ion radical and ethylene in its fragmentation, a process of which is also observed in chemical reaction. On the other hand, these facts indicate that some mass spectral fragmentations parallel chemical degradation processes and therefore also parallel retroprocesses of synthetic reactions of organic compounds.



⟹ means mass spectral fragmentation process

⟶ indicates chemical reaction

On this consideration, we have succeeded a total synthesis of a protoberberine alkaloid xylopinine (1) as shown in the following chart. Thus, the mass spectrum of xylopinine (1) shows an ion (3) having an o-quinodimethane system together with a 3,4-dihydroisoquinolinium ion (2).[7] This fragment process suggests that a combination of synthons corresponding to the two ions 2 and 3 would give xylopinine 1 by a retro-process of mass spectral pattern. In fact, heating an equimolar amount of the 3,4-dihydroisoquinoline 2 and the benzocyclobutenol 5,[8] a synthon of the ion 3 gave in a nice yield the expected protoberberine 4 which on reduction afforded xylopinine 1.[9,10]

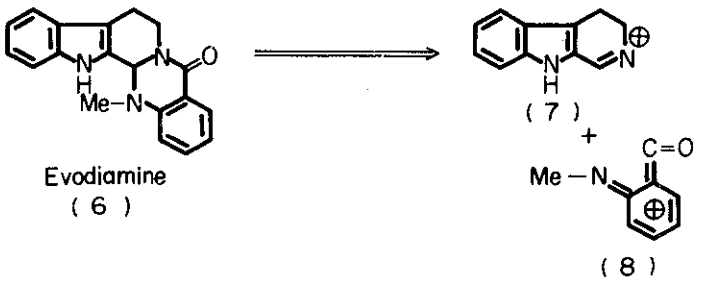


On this finding we proposed a name retro mass spectral synthesis[11] to synthetic approaches, whose analysis is based on fragmentation process in the mass spectrum used widely in a structural determination of organic compounds.

In this paper, we wish to describe the syntheses of quinazoline alkaloids and benzoxazinone by retro mass spectral synthesis which uses anthranilic acid and salicylic acid as an important starting material.

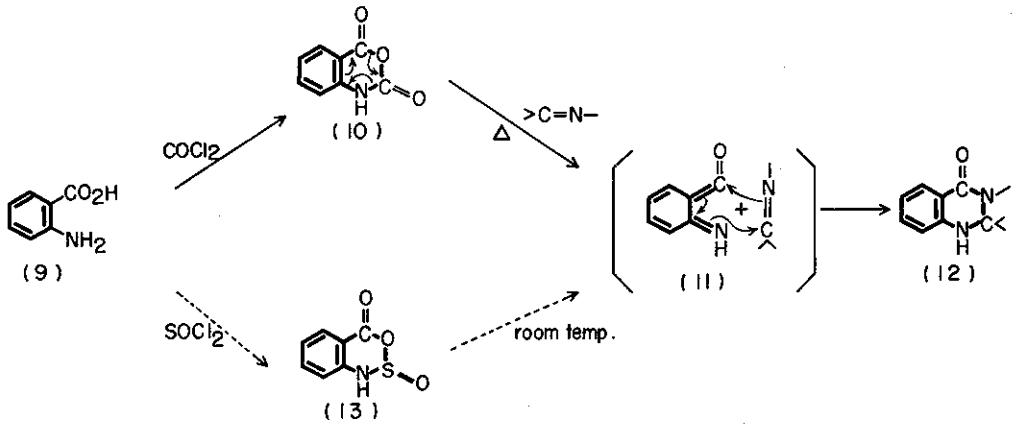
II. SYNTHESIS OF QUINAZOLONE ALKALOIDS

Mass spectral cleavage of evodiamine (6) involves a retrograde Diels-Alder type fragmentation to form two characteristic ions, the 3,4-dihydro-β-carboline (7) and iminoketene 8. Since some kind of ($_{\pi}4 + _{\pi}2$)cycloaddition is a reversible reaction,[12] we planned a new synthetic procedure for evodiamine (1) from synthons 7 and 8, which would correspond to the fragment ions in the mass spectrum of 6.



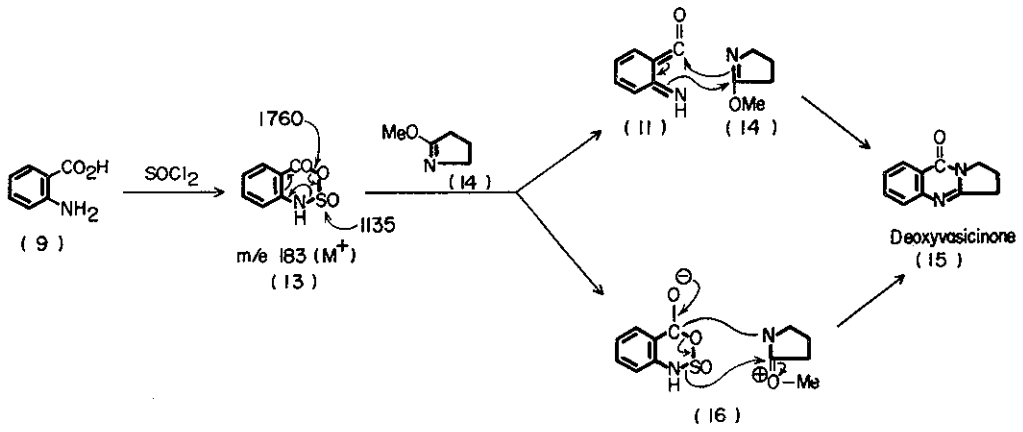
First, we investigated a synthesis of the iminoketene 8, whose reaction with cyclic imines was carried out as a model experiment as follows.

It has been well known that the reaction of anthranilic acid (9) hydrochloride with phosgene afforded isatoic anhydride (10),[13] whose condensation with imines was investigated under severe condition.[14] Since the mechanism had not been reported in the above reaction, we assumed that an intermediate would be iminoketene 11, 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 13 was used as a possible precursor of 11.



Heating anthranilic acid (9) with thionyl chloride in dry benzene under reflux gave the unstable sulfinamide anhydride 13[15] as a pale yellow viscous oil. The reaction of sulfinamide anhydride 13 with O-methylpyrrolidone (14), which was unstable on heating, was carried out in dry benzene at room temperature for 1 - 2 h to afford regiospecifically deoxyvasicinone (15)[16] in good yield, identical with an authentic sample by comparison of

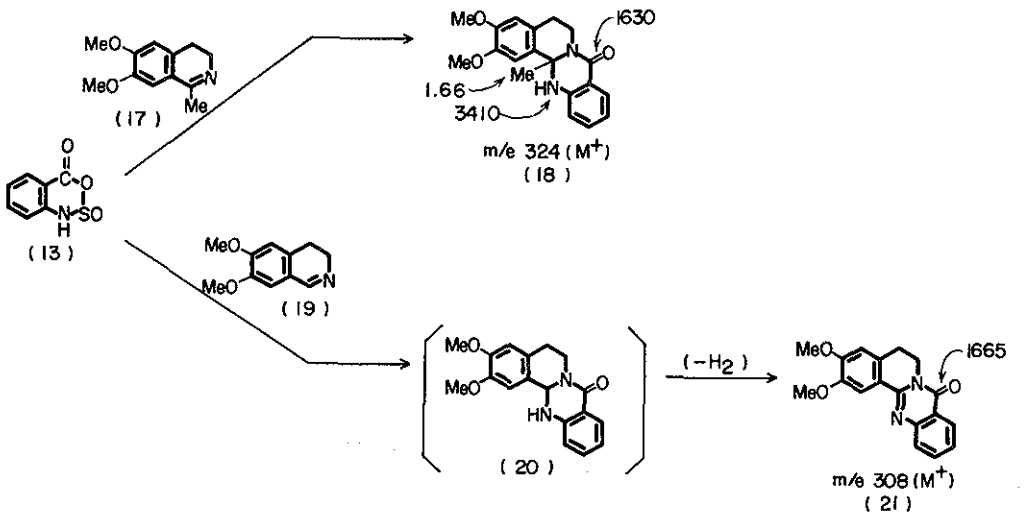
reported data. In this reaction, the sulfinamide anhydride 13 could have been converted into the iminoketene 11, which would regiospecifically react with 14 by a concerted ($_{\pi}4 + _{\pi}2$) cycloaddition pattern to form deoxyvasicinone (15). However, since the anhydride 13 is prepared by heating at 80° without decomposition to the iminoketene 11, a stepwise mechanism via the intermediate 16 is also likely.[17]



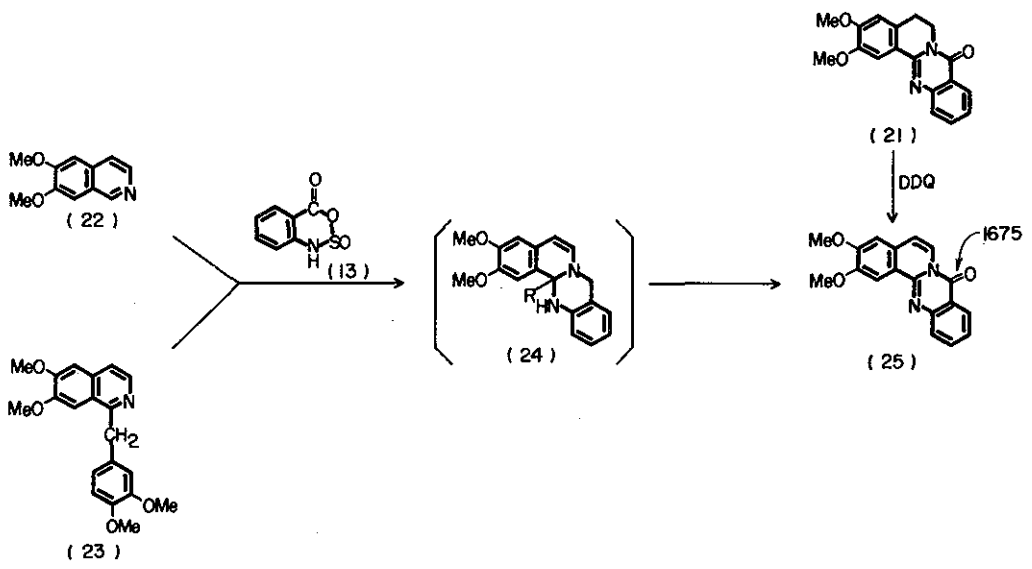
(9) (13) (14) (11) (14) (15) (16)

On the basis of this fact, we investigated a reaction of the anhydride 13 with 3,4-dihydroisoquinolines and isoquinoline derivatives. Before investigation of a synthesis of evodiamine it is examined whether this type of a cycloaddition of the iminoketone with imines would give a quinazolone system or not. Regiospecific cycloaddition of 13 with 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline (17) in dry benzene at room temperature gave 5,6,7,8,13,13a-hexahydro-2,3-dimethoxy-8-oxoisoquinolo[1,2-b]quinazoline (18), whose structure was easily determined by its ir, mass and nmr

spectroscopy. On the other hand, the same reaction of 13 with the 3,4-dihydroisoquinoline 19 afforded the 5,6,7,8-tetrahydro-8-oxo-isoquinoloquinazoline (21) by a spontaneous dehydrogenation of the initial product (20).[17]

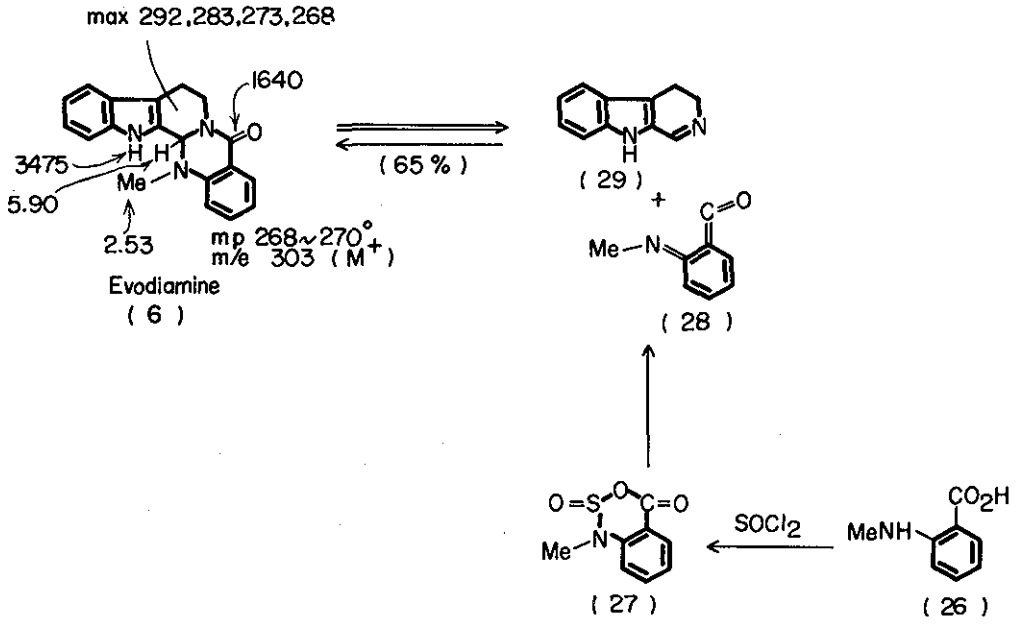


Similar reaction of 6,7-dimethoxyisoquinoline (22), followed by spontaneous dehydrogenation of the first formed product 24 gave the 7,8-dihydro-8-oxoisoquinoloquinazoline (25), which was also obtained by a dehydrogenation of the tetrahydro compound 21 with 2,3-dichloro-5,6-dicyano-p-quinone in boiling benzene. Surprisingly, in the reaction of papaverine (23) with 13, 7,8-dihydro-2,3-dimethoxy-8-oxoisoquinolino[1,2-a]quinazoline (25) was obtained during the reaction of which a debenzylation of the initially formed compound 24 occurred.[17]

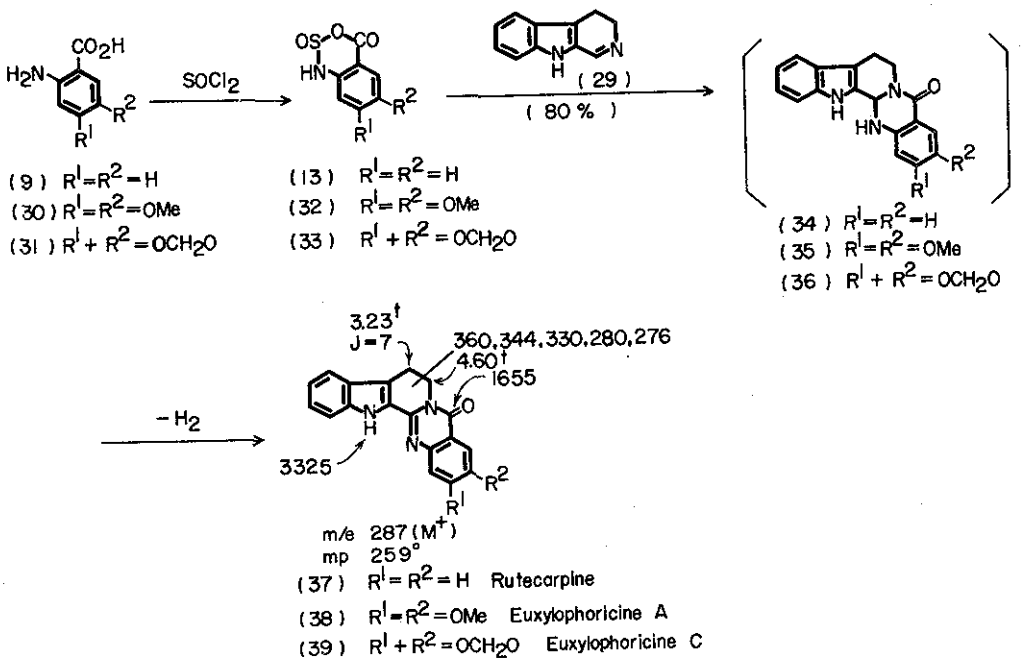


Thus we have developed a novel regiospecific synthesis of the quinazolone system by a cycloaddition of imines or imino-ethers with iminoketene derived from anthranilic acid, and then, on the basis of this finding, we examined a synthesis of evodiamine by retro mass spectral synthesis.

Heating N-methylanthranilic acid (26) with thionyl chloride in dry benzene gave an unstable sulfinamide anhydride 27, which on treatment with 3,4-dihydro-β-carboline (29) in dry benzene at room temperature evolved sulfur dioxide to afford regiospecifically evodiamine 6 in 65 % yield, perhaps via a hypothetical intermediate 28. In this reaction, both 3,4-dihydro-β-carboline 29 and iminoketene 28 correspond to the fragment ions in mass spectrum of evodiamine 6.[17] The ir, uv, and nmr spectra of our product were superimposable upon those of the natural product 6.[18]



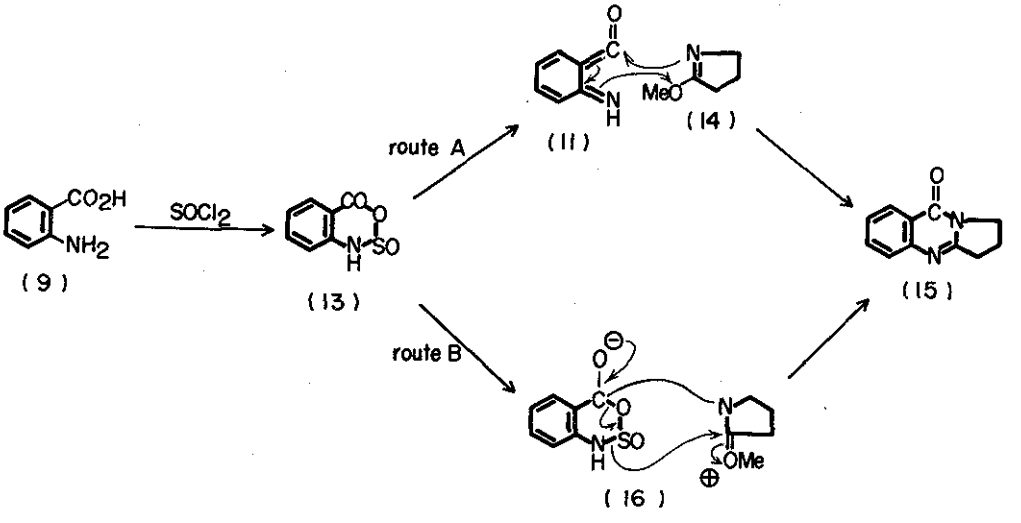
In a similar manner, rutecarpine (37) was also obtained in one step. Namely, treatment of the sulfinamide anhydride (13), derived from anthranilic acid (9) and thionyl chloride, with 3,4-dihydro-β-carboline (29) in dry benzene at room temperature gave, in 80 % yield, rutecarpine (37) by a spontaneous dehydrogenation of the initial product 34 in the same way as the case of the isouqinoline series mentioned above.[17] Our product showed spectral data as shown in the following chart and was identical with natural rutecarpine[19] in ir, uv, and nmr spectral comparisons.



Moreover 6-amino-3,4-dimethoxybenzoic acid (30) was converted, by heating with thionyl chloride in dry benzene, into the sulfinamide anhydride (32), which was condensed with 3,4-dihydro-β-carboline (29) at room temperature in dry benzene to afford euxylophoricine A (38) through the dihydro intermediate (35), which was found in Euxylophora paraësis. Euxylophoricine C (39) was also synthesised by the condensation of 3,4-dihydro-β-carboline (29) with the sulfinamide anhydride (33), derived from 6-amino-3,4-methylenedioxybenzoic acid (31).[20]

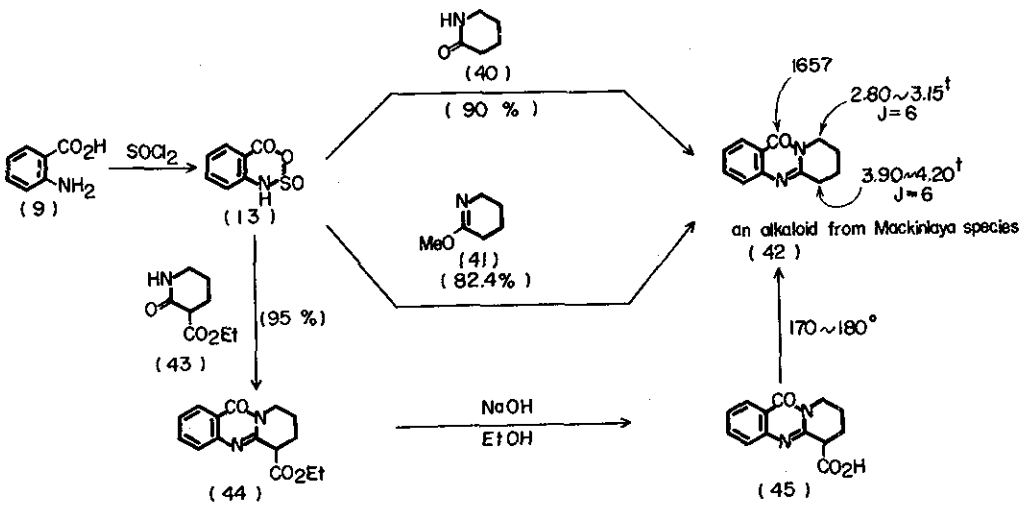
As mentioned above, we have developed a new and one-step synthesis of quinazolone system (15) by a cycloaddition of the iminoketene 11, generated *in situ* from anthranilic acid (9) via the sulfinamide anhydride (13), to imine system (14), and this reaction

has been applied to a total synthesis of evodiamine and rutecarpine along retro mass spectral synthesis. Although we have proposed a concerted reaction mechanism in this type of cycloaddition reaction along the route A, a stepwise mechanism by the route B is likely. If the latter mechanism would contribute, the formation of quinazolines from the reaction of the iminoketene with amides would be possible. Based on this premise, we have investigated the reaction of the sulfinamide anhydride with several amides.

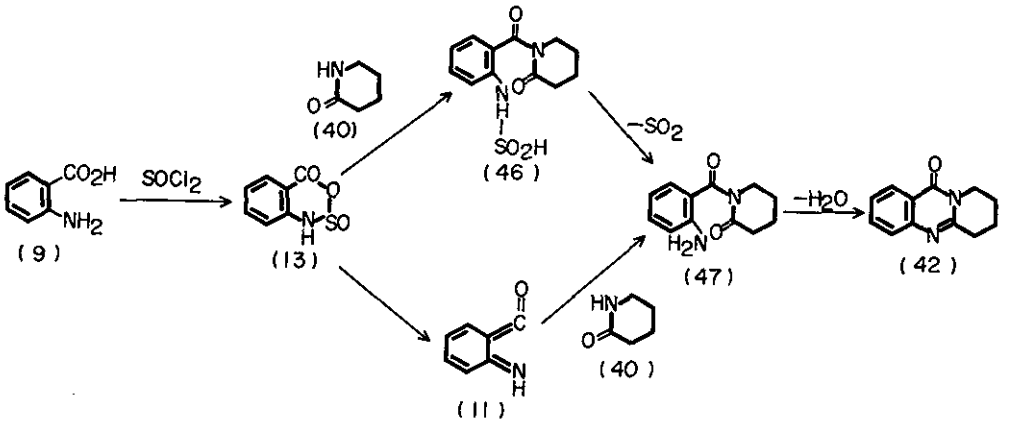


Firstly, the sulfinamide anhydride 13 was treated with 2-piperidone (40) in dry benzene at room temperature overnight to give the condensation product in 90 % yield, whose ir and nmr spectra indicated this product to be 6,7,8,9-tetrahydropyrido[2,1-b]quinazolin-11-one (42). This structure was proved by direct comparisons with the authentic sample, prepared in 82.4 % yield by our method[17] from the sulfinamide anhydride 13 and O-methylpiperidone (41) by

melting point and spectral comparisons.[21] Thus we have developed a convenient synthesis of quinazolone derivatives from anthranilic acid and the amides and also achieved a simple total synthesis of an alkaloid (42) from Mackinlaya species isolated by Fitzgerald. The reaction of 13 with the lactam ester 43, which has two reaction sites, proceeded only in amide function to give the quinazolone-6-carboxylate 44 in 95 % yield.[20,21] This product was converted into the quinazolone 42 by mild hydrolysis with 5 % ethanolic sodium hydroxide, followed by decarboxylation of the resulting carboxylic acid 45 at 170 - 180°.[21]

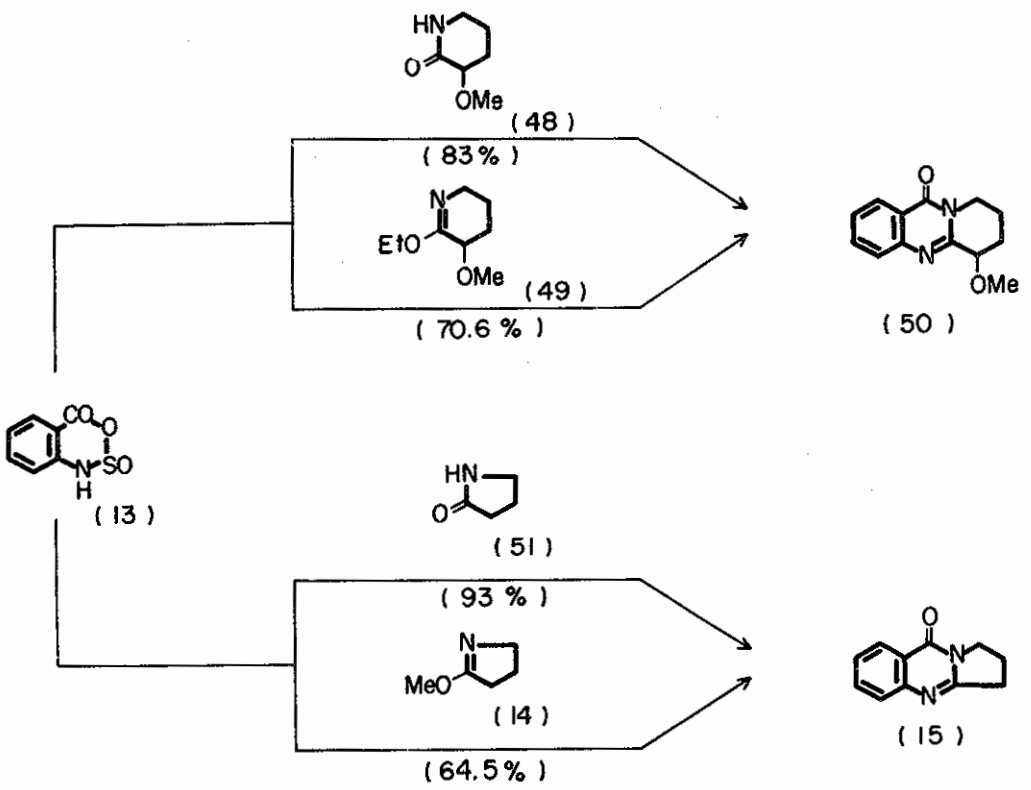


This reaction could proceed stepwise via an intermediate 47 which formed through the intermediate 46 or by a condensation of the lactam 40 with the iminoketene 11, generated in situ from the sulfinamide anhydride (13).[21]



Similarly, 3-methoxypiperidone (48) reacted with the sulfinamide anhydride 13 in dry benzene at room temperature to form 6,7,8,9-tetrahydro-6-methoxypyrido[2,1-b]quinazolin-11-one (50) in 83 % yield, which was also prepared in 70.6 % yield by cycloaddition of 13 to the imine 49.[21]

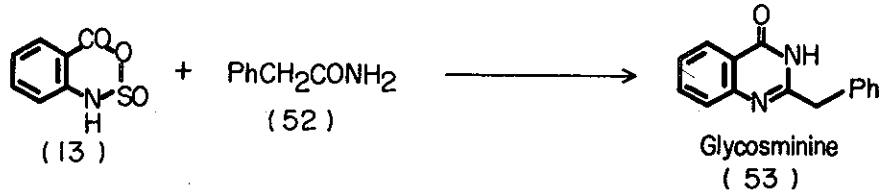
The fact that the reaction of the lactams 48 with 13 proceeded in higher yield than that of the lactim ether 49 as shown in the following chart indicates that this new synthesis of quinazolones is an effective method. Moreover, deoxyvasicinone (15) was also obtained in 93 % yield from pyrrolidone 51, but the yield in a synthesis of 15 from the corresponding lactim ether 14 was 64.5 %.[21]



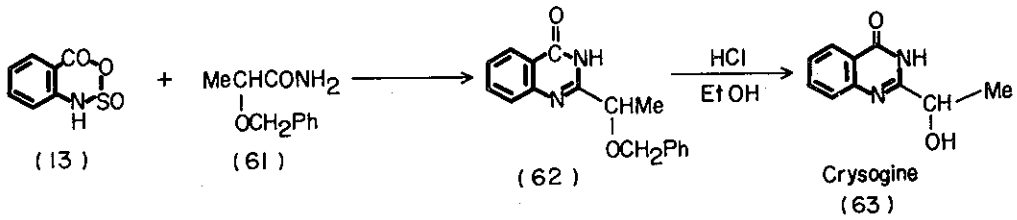
Secondly, we investigated the condensation of a noncyclic amide with the sulfinamide anhydride 13 on the ground of the above finding. Thus, treatment of phenylacetamide (52) with sulfinamide anhydride 13 in dry benzene at room temperature gave, in 39.5 % yield, 2-benzylquinazolin-4-one (53), which was identical with glycosminine found in Glycosmis arborea as a minor alkaloid.[21]

By the same method, alkaloids, glycorine (57),[20] glomerine (58),[20] homoglomerine (59)[20] and arborine (60),[21] were also synthesized in a moderate yield by a condensation of amides 54, 55, 56 and 52 with the N-methylsulfinamide anhydride 27 in dry chloro-

form, respectively, and physical data of our product were identical with reported ones.

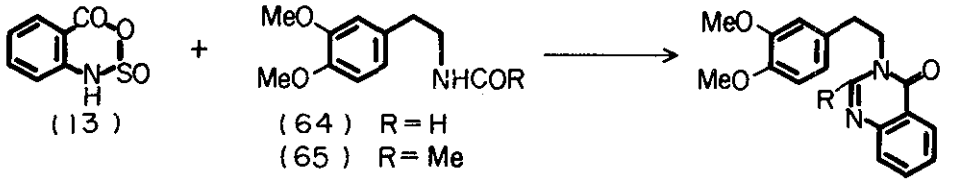


Furthermore, treatment of the sulfinamide anhydride (13) with (±)-O-benzyllactamide (61) under the similar conditions gave (±)-O-benzylcrysogine (62). Debenzylation of this by refluxing with hydrochloric acid in ethanol gave (±)-crysogine (63),[20] whose levorotatory isomer was obtained from a culture broth of Penicillium chrysogenium.



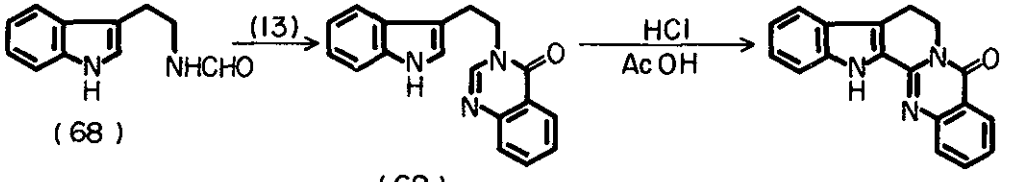
N-Phenethylformamide (64) and N-phenethylacetamide (65) also reacted with the sulfinamide anhydride 13 in dry benzene to afford the corresponding 3-phenethylquinazolin-4-ones 66 and 67 in 89 and 84 % yield, respectively.

On the basis of the finding that 3-phenethylquinazolones have been prepared from N-formylphenethylamine, we examined an alternative synthesis of rutecarpine (37) by this method. A condensation of N-formyltryptamine (68) with the sulfinamide anhydride



(13) (64) R=H (65) R=Me (66) R=H (67) R=Me

(13) was carried out in a mixture of dry benzene and chloroform at room temperature for 2 h to give, in 63 % yield, 3-indolylethylquinazolin-4-one (69). This product was heated with concentrated hydrochloric acid in acetic acid at 110° for 166 h to afford rutecarpine (37), in 45 % yield, whose ir, uv, and nmr spectra were superimposable upon those of the authentic sample.[21]



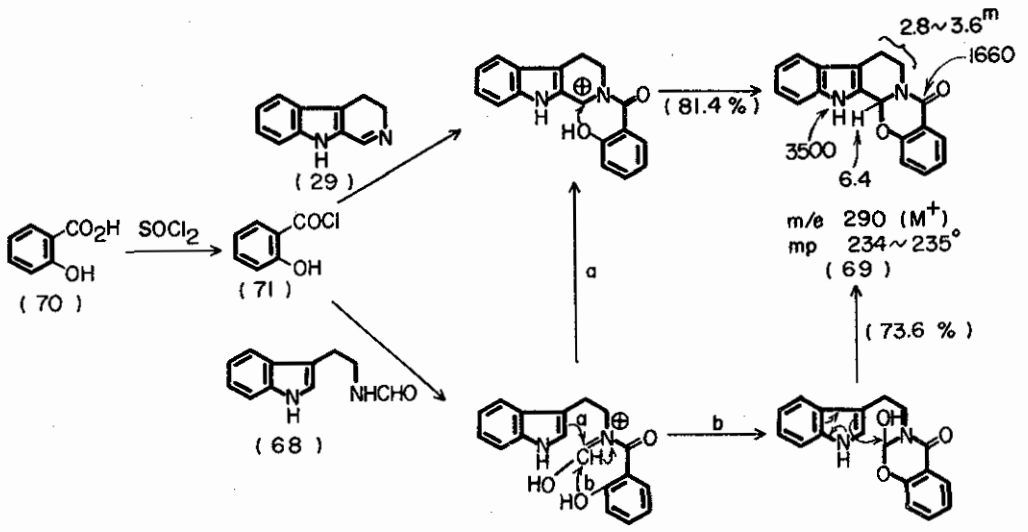
(68) (69) Rutecarpine (37)

Thus we have developed a new synthetic method for quinazolones, whose reaction could be applied to a syntehsis of the quinozolone derivatives having various substituents at a given position.

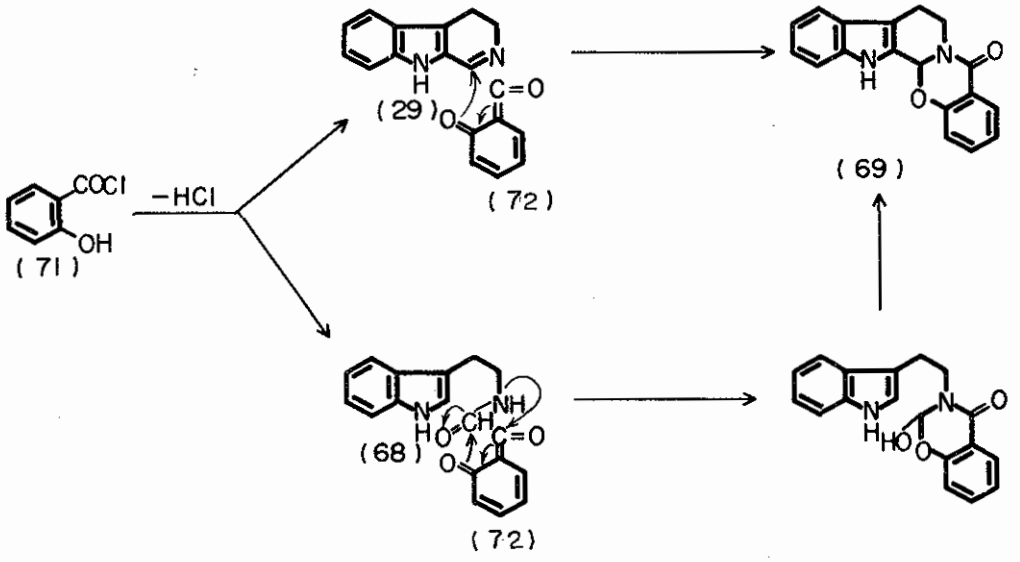
III. SYNTHESIS OF BENZOXAZINONE DERIVATIVES

Finally, we examined a reactivity of salicylic acid (70), instead of anthranilic acid (9), in order to find a novel and simple synthetic method for 1,3-benzoxazin-4-one system by the reaction with imines or amide.

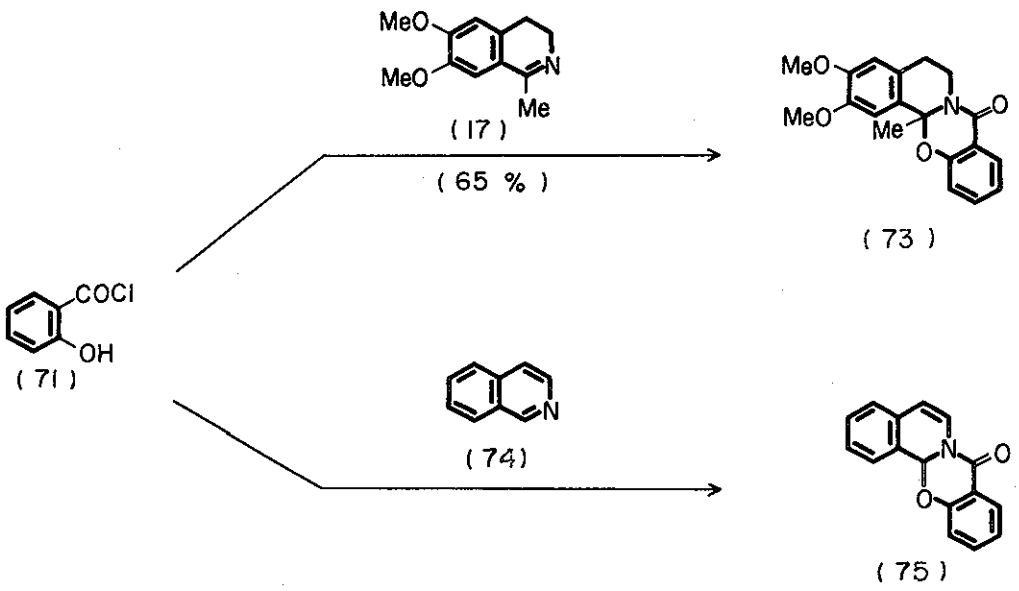
Heating salicylic acid (70) with an excess of thionyl chloride in dry benzene in a current of nitrogen for 4 h gave salicyl chloride (71),[22] whose treatment with an equimolar amount of 3,4-dihydro-β-carboline (29) in dry benzene at room temperature for 2 h, afforded the condensation product in 81.4 % yield. The ir, nmr and mass spectra indicated this compound to be indolopyridobenzoxazin-4-one (69). Treatment of salicyl chloride (71) with 1.2 molar equivalent of N-formyltryptamine (68) in dry benzene and chloroform under the same conditions as above gave, in 73.6 % yield, the indolopyridobenzoxazepine (69) which was identical with the authentic sample, prepared from 29, in spectral and mp comparisons.[23] These reaction would proceed as shown in the following chart.



However, the following mechanism would not be ruled out; salicyl chloride (71) might be firstly converted into the more reactive oxoketene (72) by an intramolecular elimination of hydrogen chloride and then the oxoketene would react with 3,4-dihydro-β-carboline (29) or N-formyltryptamine (68) in a manner due to an intermolecular cycloaddition as indicated in the following chart.[23]



3,4-Dihydro-6,7-dimethoxy-1-methylisoquinoline (17) reacted with salicyl chloride (71) in dry benzene at room temperature for 16 h to form the corresponding 1,3-benzoxazin-4-one (73) in 65 % yield. Similarly, the reaction of isoquinoline (74) with 70 in dry benzene under the same conditions afforded, in 75 % yield, the isoquinolobenzoxazinone (75).[23]



IV. CONCLUSION

As mentioned above, we have developed a novel and simple synthetic procedure for quinazolone and 1,3-benzoxazin-4-one systems, and a further extension of this reaction is now in progress. In our opinion synthetic method should be one-step or very simple and facile one and, furthermore, synthesis would be hoped to be carried out at room temperature. From the above point of view, retro mass spectral synthesis is very interesting for us.

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