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SIMPLE SYNTHESIS OF QUINAZOLONE ALKALOIDS ARBORINE AND RUTECARPINE THROUGH IMINOKETENE

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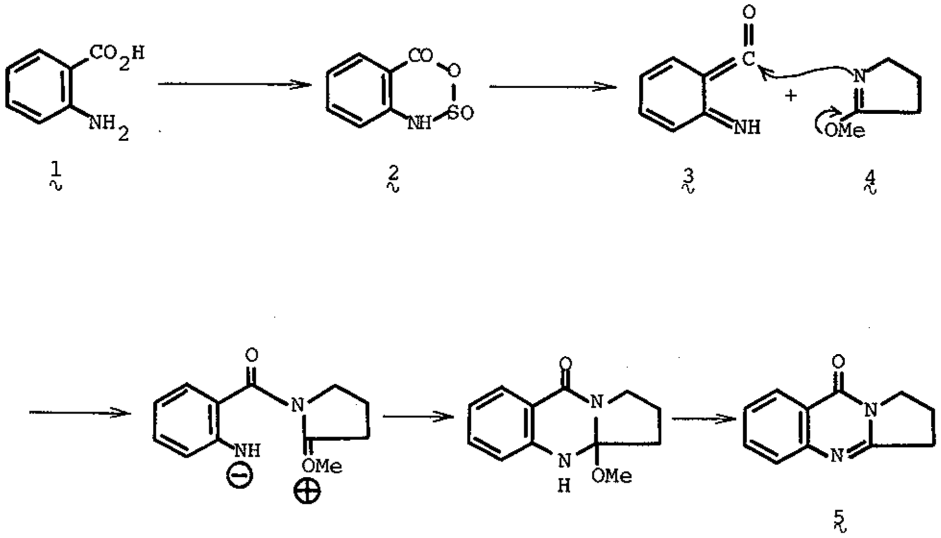
The iminoketene (3) generated *in situ* from the sulfinamide anhydride (2), prepared from anthranilic acid (1), reacted with several types of amide to give quinazolin-4-ones (12 ∿ 14). This reaction was applied to a total synthesis of arborine (19) and rutecarpine (22).

In previous papers[1,2], we have reported a novel one-step synthesis of quinazolones (5) by a cycloaddition reaction of the iminoketene (3), generated *in situ* from anthranilic acid (1) through the sulfinamide anhydride (2), to imines (4) and also a total synthesis of evodiamine and rutecarpine by this reaction along the retro mass spectral synthesis. If this reaction would proceed by way of a stepwise mechanism as shown in the following scheme, the amide could react with an iminoketene to form quinazolone. Based on this idea, we have investigated a reaction of 3 with several types of amide and here wish to report our successful results.

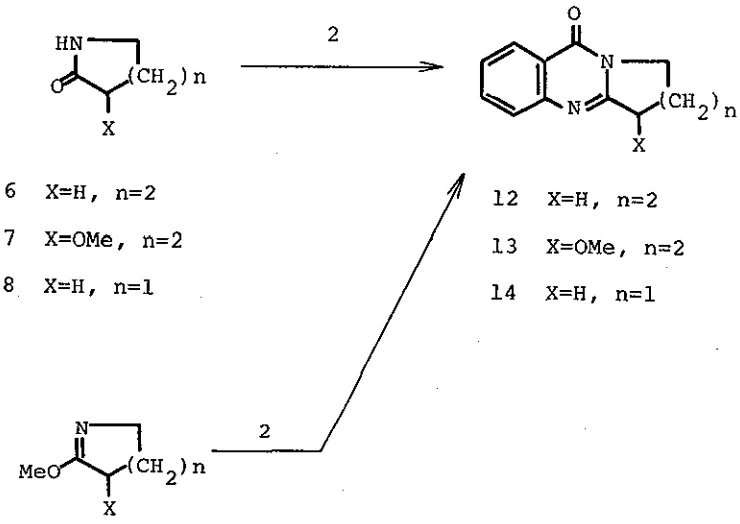
Scheme 1



The sulfinamide anhydride (2), prepared form anthranilic acid (1) and thionyl chloride in dry boiling benzene, was treated with 2-piperidone (6) in dry benzene at room temperature overnight to give a condensation product, mp 99 ∿ 99.5°C, in 90 % yield, whose ir [ν_{max} ($CHCl_3$) 1657 cm^{-1}] and nmr spectra [δ ($CDCl_3$) 1.70 ∿ 2.30 (4H, m), 2.80 ∿ 3.15 (2H, t, J 6 Hz), 3.90 ∿ 4.20 (2H, t, J 6 Hz), 7.10 ∿ 7.90 (3H, m) and 8.20 (1H, dd, J 2 and 8 Hz)] indicated this compound to be 6,7,8,9-tetrahydropyrido[2,1-b]quinazolin-11-one (12). This structure was proved by direct comparisons with the authetic sample, prepared in 82.4 % yield by the previous method[1] from 2 and O-methylpiperidone (9), by melting points (lit.,[3] mp 98.5 ∿ 99.5°C) and spectral comparisons. Thus we have developed a simple synthesis of quinazolone from anthranilic acid and amide, and also achieved a total synthesis of an alkaloid from *Mackinlaya* species.[3]

Similarly, 3-methoxypiperidone (7) and pyrrolidone (8) reacted with 2 in dry benzene at room temperature to afford the corresponding quinazolones [13, oil, m/e 230 (M^+) and 14, mp 196 ∿ 198°C (lit.[1,2], mp 196 ∿ 198°C)] in 83 % and 93 % yields, respectively, both of which were also prepared by treatment of 2 with lactim ethers (10 and 11) in 70.6 % and 64.5 % yield, respectively.

Scheme 2



6 X=H, n=2
7 X=OMe, n=2
8 X=H, n=1

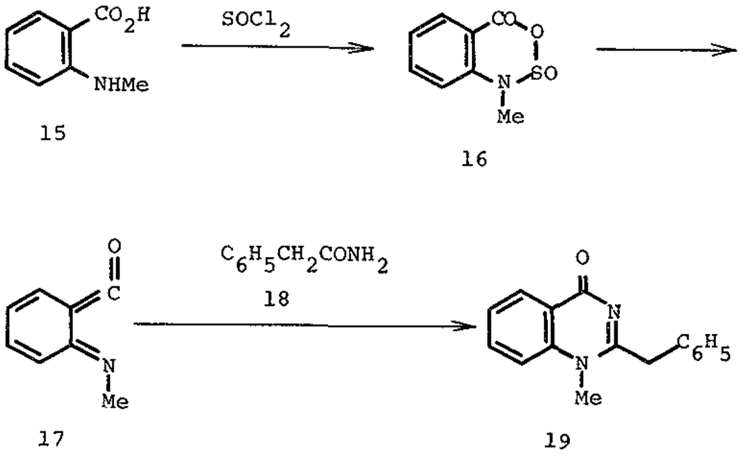
12 X=H, n=2
13 X=OMe, n=2
14 X=H, n=1

9 X=H, n=2
10 X=OMe, n=2
11 X=H, n=1

The fact that the reaction of lactams (6, 7 and 8) with 2 proceeded in higher yield than that of lactim ethers (9, 10 and 11) indicates this new reaction to be an effective synthetic method for quinazolone derivatives.

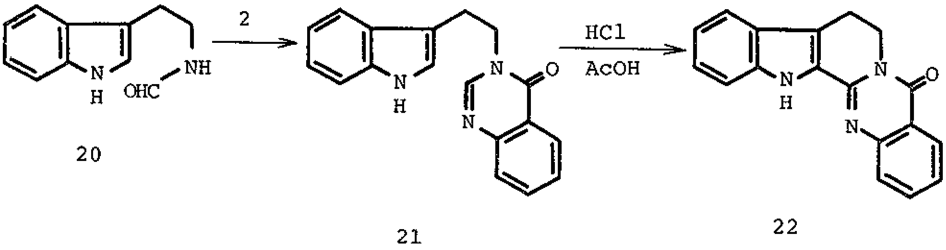
On the basis of this finding, we examined a total synthesis of quinazolone alkaloids. Thus, treatment of phenylacetamide (18) with sulfinamide anhydride (16)[1,2], prepared from N-methylanthranilic acid (15) and thionyl chloride in dry boiling chloroform, gave arborine (19), mp 154 ∿ 156°C (lit.,[4] mp 155 ∿ 156°C), m/e 250 (M^+), an alkaloid from *Glycosmis arborea*,[4] in 33 % yield through the iminoketene (17), whose melting point and nmr [δ($CDCl_3$) 3.60 (3H, s, NMe), 4.26 (2H, s, CH_2), 7.10 ∿ 7.90 (8H, m, ArH) and 8.30 (1H, dd, *J* 8 and 2 Hz, C_8-H)] and mass [m/e 250 (M^+), 249, 133, 132, 105 and 104] spectral data were identical with those of natural one.[4,5]

Scheme 3



Furthermore, a condensation of N-formyltryptamine (**20**) with the sulfinamide anhydride **2** was carried out in dry benzene and chloroform at room temperature for 2 hr to give, in 63 % yield, 3-indolylethyl-4-quinazolone (21), mp 164 ∿ 165°C [ν_{max} ($CHCl_3$) 3480 (NH) and 1660 (CO) cm^{-1}; δ($CDCl_3$) 3.25 (2H, t, J 7 Hz $C\underline{H}_2CH_2N$), 4.25 (2H, t, J 7 Hz, $CH_2C\underline{H}_2N$), 6.75 (1H, broad s, indole α-H), 7.0 ∿ 7.7 (8H, m, 7 x ArH and >N-C$\underline{H}$=N-) and 8.20 (1H, dd, J 8 and 2 Hz, C_5-H), m/e 289 (M^+)]. This product was heated with concentrated hydrochloric acid and acetic acid[6] at 110°C for 166 hr to afford, in 45 % yield, rutecarpine (**22**), mp 259°C (lit.,[1,2] mp 259°C), an alkaloid from Evodia rutecarpa[7], whose ir, uv and nmr spectra were superimposable upon those of the authentic sample.[1,2]

Scheme 4



Thus, we have developed a new and simple synthetic method for quinazolones and a further development of this reaction is now in our hand.

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