Iminoketene Cycloaddition. 1. A Facile Synthesis of Quinazolone System by Condensation of Iminoketene with Imines—A Total Synthesis of Evodiamine and Rutecarpine by Retro Mass-Spectral Synthesis

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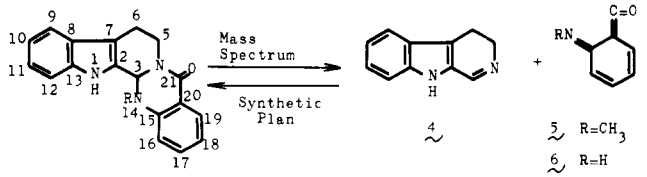
Abstract: Cycloaddition of the iminoketene **6**, derived from anthranilic acid (**7**), with 3,4-dihydro-6,7-dimethoxyisoquinoline (**16**), followed by dehydrogenation, gave 7,8-dihydro-2,3-dimethoxy-8-oxoisoquinolo[1,2-*b*]quinazoline (**23**), which was also obtained from papaverine (**21**) or 6,7-dimethoxyisoquinoline (**20**). Moreover, this paper reports a total synthesis of evodiamine (**1**) and rutecarpine (**3**).

Recently, a systematic method available for the synthesis of complicated compounds has been discussed[3] and Corey has developed a computer-assisted synthetic analysis, which allowed the automatic processing of a target molecular structure in the retrosynthesis.[4] We have also been interested in a development of an effective way for the synthesis of complex molecules[5] and here wish to report our new synthetic approach, which we call "retro mass-spectral synthesis", based on a fragmentation process in the mass spectrum used widely in a structural determination of organic compounds.

Mass spectral cleavage of evodiamine (**1**) involves a retrograde Diels–Alder type fragmentation to form two characteristic ions, the 3,4-dihydro-β-carboline (**4**) ion and iminoketene **5** ion. Since some kind of ($_\pi4 + _\pi2$) cycloaddition is a reversible reaction,[6] we planned a new synthetic procedure for evodiamine (**1**) from synthons **4** and **5**, which would correspond to the fragment ions in the mass spectrum of **1** (see Scheme I).

Scheme I

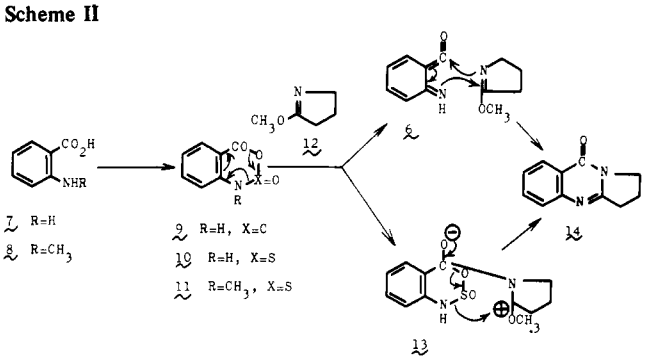


1 R=CH_3
2 R=H
3 3,14-dehydro form of 2
4
5 R=CH_3
6 R=H

First, we investigated a synthesis of the iminoketene **6**, whose reaction with cyclic imines was carried out as a model experiment. It has been well known that the reaction of anthranilic acid (**7**) hydrochloride with phosgene[7] afforded isatoic anhydride (**9**), whose condensation with imines was investigated under severe condition.[8] Since the mechanism had not been reported in the above reaction, we assumed that an intermediate would be iminoketene **6**, formed by an elimination of carbon dioxide by a retrograde Diels–Alder type reaction as shown in Scheme II. In our case cycloaddition reaction with imines would be hoped to proceed under mild conditions and, therefore, sulfinamide anhydride **10** was used as a possible precursor of **6**.

Heating anthranilic acid (**7**) with thionyl chloride in dry benzene under reflux gave the unstable sulfinamide anhydride **10**[9] as a pale yellow viscous oil [*m/e* 183 (M^+) and 119 (C_7H_5NO, base peak); ν_{max} ($CHCl_3$) 1760 (-CO-O-CO-) and 1135 cm^{-1} (-SONH-)]. The reaction of **10** with *O*-methylpyrrolidone (**12**),[10] which was unstable on heating, was carried out in dry benzene at room temperature for 1–2 h to afford regiospecifically deoxyvasicinone (**14**) in good yield, identical with an authentic sample[11] by comparison of reported data. In this reaction, the sulfinamide anhydride **10** could have been converted into the iminoketene **6**, which would regiospecifically react with **12** by a concerted ($_\pi4 + _\pi2$) cycloaddition pattern to form deoxyvasicinone (**14**). However, since the anhydride **10** is prepared by heating at 80 °C without decomposition to the iminoketene **6**, a stepwise mechanism via the intermediate **13** is likely.

Scheme II

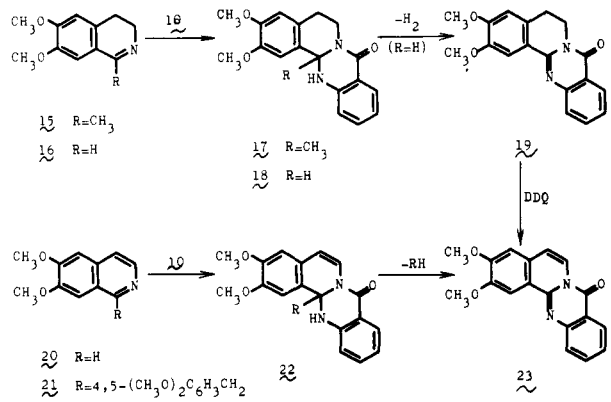


On the basis of this fact, we investigated a reaction of the anhydride **10** with 3,4-dihydroisoquinolines **15** and **16** and isoquinoline derivatives **20** and **21**. Regiospecific cycloaddition of **10** with 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline (**15**) in dry benzene at room temperature gave 5,6,7,8,13,13a-hexahydro-2,3-dimethoxy-8-oxoisoquinolo[1,2-*b*]quinazoline (**17**) [*m/e* 324 (M^+)], whose structure was easily determined by its ir (ν_{max} 3410 and 1630 cm^{-1}) and NMR spectroscopy [δ 1.66 (3 H, s, Me)]. On the other hand, the same reaction of **10** with the 3,4-dihydroisoquinoline **16** afforded the 5,6,7,8-tetrahydro-8-oxoisoquinoloquinazoline (**19**) [*m/e* 308 (M^+)] by a spontaneous dehydrogenation of the initial product **18**, which showed an amide carbonyl group at 1665 cm^{-1} in its ir spectrum, and the NMR spectrum revealed two methylene protons at δ 3.06 and 4.45 as triplets having J = 8 Hz.

Similar reaction of 6,7-dimethoxyisoquinoline (**20**), followed by spontaneous dehydrogenation gave the 7,8-dihydro-8-oxoisoquinoloquinazoline (**23**) [*m/e* 306 (M^+), ν_{max} 1675 cm^{-1}], which was also obtained by a dehydrogenation of the tetrahydro compound **19** with 2,3-dichloro-5,6-dicyano-*p*-

quinone in boiling benzene. Surprisingly, in the reaction of papaverine (**21**) with **10**, 7,8-dihydro-2,3-dimethoxy-8-oxoisoquinolino[1,2-*b*]quinazoline (**23**) was obtained, during the reaction of which a debenzylation of the initially formed compound **22** occurred (see Scheme III).

Scheme III



Thus we have developed a novel regiospecific synthesis of the quinazolone system by a cycloaddition of imines with **10** or iminoketene derived from anthranilic acid, and then, on the basis of this finding, we examined a synthesis of evodiamine (**1**) by retro mass-spectral synthesis.

Heating *N*-methylanthranilic acid (**8**) with thionyl chloride in dry benzene gave an unstable sulfinamide anhydride **11**, which, on treatment with 3,4-dihydro-β-carboline (**4**) in dry benzene at room temperature evolved sulfur dioxide to afford regiospecifically evodiamine (**1**) [mp 268–270 °C; *m/e* 303 (M^+)] in 65% yield, perhaps via a hypothetical intermediate **5**. The ir (ν_{max} 3475 and 1640 cm^{-1}), uv (λ_{max} 292, 283, 273, and 268 nm), and NMR [δ 2.53 (3 H, s, NMe) and 5.90 (1 H, s, C3–H)] spectra of our product were superimposable upon those of the natural product.[12]

In a similar manner, rutecarpine (**3**) was also obtained in one step. Namely, treatment of the sulfinamide anhydride **10** with 3,4-dihydro-β-carboline (**4**) in dry benzene at room temperature gave, in 80% yield, rutecarpine (**3**) [mp 259 °C; *m/e* 287 (M^+)] by a spontaneous dehydrogenation of the initial product **2** in the same way as the case of the isoquinoline series. Our product was identical with natural rutecarpine[12] in ir (ν_{max} 3325 and 1655 cm^{-1}), uv (λ_{max} 360, 344, 330, 288, and 276 nm), and NMR [δ 3.23 and 4.60 (each 2 H, t, J = 7 Hz)] spectral comparisons.

The consideration of mass spectra provides an effective route for the elaboration of a synthetic scheme.

Experimental Section

All melting points are uncorrected. Ir and uv spectra were measured with Hitachi 215 and Hitachi 124 recording spectrometers, respectively. NMR spectra were taken with a JNM-PMX-60 spectrophotometer and mass spectra with a Hitachi RMU-7 mass spectrometer.

Deoxyvasicinone (14). A mixture of 300 mg of anthranilic acid (**7**) and 3.0 g of thionyl chloride in 15 ml of dry benzene was refluxed for 2 h in a current of nitrogen, then an excess of reagent and solvent was distilled off in vacuo at 18–20 °C to leave a pale yellow syrup, to which was added a solution of 198 mg of 2-methylpyrrolidone (**12**) in 20 ml of dry benzene in one portion at room temperature, and the mixture was allowed to stand for 1–2 h at room temperature to give a white solid. After evaporation of solvent, the residue was dissolved in chloroform. The extract was washed with 5% sodium bicarbonate aqueous solution and water, dried over sodium sulfate, and evaporated to give 240 mg (64.5%) of deoxyvasicinone (**14**) as colorless needles after recrystallization from ethanol: mp 196–198 °C; ir ($CHCl_3$) 1660 cm^{-1} (C=O); NMR ($CDCl_3$) δ 2.25 (2, H, m, $NCH_2CH_2CH_2$), 3.25 (2 H, t, J = 8 Hz, $NCH_2CH_2CH_2$), 4.25 (2 H, t, J = 7 Hz, NCH_2), and 7.5 (4 H, m, ArH). The spectral data were identical with reported ones by Onaka.[11]

5,6,7,8,13,13a-Hexahydro-2,3-dimethoxy-8-oxoisoquinolo[1,2-*b*]quinazoline (17). To sulfinamide anhydride **10** [obtained from 274 mg of anthranilic acid (**7**)] was added 205 mg of 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline (**15**) in 60 ml of dry benzene. The resulting mixture was set aside overnight at room temperature. Unreacted isoquinoline was recovered by filtration to afford a clear solution, which was washed with 10% sodium carbonate, water, and dried over potassium carbonate. Evaporation of the solvent afforded 70 mg of a brown residue, which was submitted to preparative chromatography with chloroform–ethanol (98:2) as solvent to give 30 mg of a solid, whose recrystallization from chloroform–ethanol yielded 10 mg of the expected product **17** as colorless needles: mp 206–207 °C; ir ($CHCl_3$) 3410 (NH) and 1630 cm^{-1} (C=O); mass *m/e* 324 (M^+); NMR ($CDCl_3$) δ 1.66 (3 H, s, CH_3), 2.46–3.20 (4 H, m, C5–H2, C6–H2), 3.80 (3 H, s, OCH_3), 3.83 (3 H, s, OCH_3), 6.50–7.46 (5 H, m, ArH), and 7.91 (1 H, m, C9–H).

Anal. ($C_{19}H_{20}N_2O_3$) C, H, N.

5,6,7,8-Tetrahydro-2,3-dimethoxy-8-oxoisoquinolo[1,2-*b*]quinazoline (19). To sulfinamide anhydride **10** [obtained from 430 mg of anthranilic acid (**7**)] was added 600 mg of 3,4-dihydro-6,7-dimethoxyisoquinoline (**16**) in 65 ml of dry benzene. The resulting mixture was allowed to stand overnight at room temperature, then washed with 10% sodium carbonate, water, and dried over potassium carbonate. Evaporation of the solvent under reduced pressure afforded a brown residue, which was recrystallized from chloroform–ether to give 730 mg (79%) of the quinazoline **19** as colorless crystals: mp 249–250 °C; ir (KBr) 1665 cm^{-1} (C=O); mass *m/e* 308 (M^+); NMR ($CDCl_3$) δ 3.06 (2 H, t, J = 8 Hz, C5–H2), 3.99 (3 H, s, OCH_3), 4.08 (3 H, s, OCH_3), 4.45 (2 H, t, J = 8 Hz, C6–H2), 6.79 (1 H, s, C4–H), and 8.50–7.32 (5 H, m, Ar*H*).

Anal. ($C_{18}H_{16}N_2O_3$) C, H, N.

7,8-Dihydro-2,3-dimethoxy-8-oxoisoquinolo[1,2-*b*]quinazoline (23).

(a) From Papaverine (21). To sulfinamide anhydride **10** [obtained from 1 g of anthranilic acid (**7**)] was added a solution of 800 mg of papaverine (**21**) in 50 ml of dry benzene. The resulting mixture was set aside at room temperature overnight, then washed with 10% sodium carbonate solution and water, dried over potassium carbonate, and evaporated to give a brown residue (1.7 g), which was submitted to silica gel column chromatography with benzene–chloroform (6:4) as eluent to afford recovered papaverine (710 mg) and 60 mg of 2,3-dimethoxy-8-oxoisoquinolo[1,2-*b*]quinazoline (**23**), which was recrystallized from chloroform–ether to yield colorless needles: mp 244–246 °C; ir (KBr) 1675 cm^{-1} (C=O); uv (EtOH) 383, 307, 277, and 247 nm; mass *m/e* 306 (M^+), 291, 263, 220, and 205; NMR ($CDCl_3$) δ 4.03 (3 H, s, OCH_3), 4.13 (3 H, s, OCH_3), 6.92 (1 H, d, J = 7 Hz, C5–H), 6.96 (1 H, s, C4–H), 7.30–7.96 (4 H, m, ArH), 8.42 (1 H, s, C1–H), and 8.56 (1 H, d, J = 7 Hz, C6–H).

Anal. ($C_{18}H_{14}N_2O_3$) C, H, N.

(b) From 6,7-Dimethoxyisoquinoline (20). To sulfinamide anhydride **10** [obtained by the same procedure as above from 274 mg of anthranilic acid (**7**)] was added 190 mg of 6,7-dimethoxyisoquinoline (**20**) in 30 ml of dry benzene. The mixture was set aside overnight, then successively washed with 10% sodium carbonate solution and water and dried over potassium carbonate. Evaporation of the solvent afforded a brown residue (310 mg), which was chromatographed on silica gel with benzene–chloroform (6:4) as eluent to afford 40 mg of 6,7-dimethoxy-8-oxoisoquinolo[1,2-*b*]quinazoline (**23**). Recrystallization of **23** from chloroform–ether yielded colorless needles, whose melting point, ir, and NMR spectral data are identical with those of the sample obtained previously.

(c) By Dehydrogenation of 19. A solution of 60 mg of 5,6,7,8-tetrahydro-2,3-dimethoxy-8-oxoisoquinolo[1,2-*b*]quinazoline (**19**) and 48.6 mg of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone in 30 ml of dry benzene was refluxed for 8 h in a current of nitrogen. Evaporation of the solvent afforded a residue which was dissolved in 10% sodium hydroxide solution and extracted with chloroform. The chloroform layer was washed with water, dried over potassium carbonate, and evaporated under reduced pressure to give 40 mg of a brown residue, which was recrystallized from chloroform–ether to yield colorless needles, mp 244–246 °C, whose melting point, ir, and NMR spectral data are identical with those of the samples obtained previously.

Evodiamine (1). A solution of 500 mg of *N*-methylanthranilic acid (**8**) and 5.0 g of thionyl chloride in 25 ml of dry benzene was refluxed for 2 h in a current of nitrogen, then an excess of reagent and solvent

was removed by distillation in vacuo at 18–20 °C to leave the sulfinamide anhydride **11** as a pale yellow syrup, to which was added a solution of 400 mg of 3,4-dihydro-β-carboline (**4**) in 10 ml of dry benzene. The mixture was allowed to stand for 1 h at room temperature. After evaporation of benzene, the residue was dissolved in chloroform, which was washed with 10% sodium hydroxide, water, and dried over sodium sulfate. Evaporation of the solvent gave 465 mg (65%) of evodiamine as pale yellow crystals after recrystallization from ethanol: mp 268–270 °C (lit.[12] mp 270–272 °C); ir ($CHCl_3$) 3475 (NH) and 1640 cm^{-1} (C=O); uv (MeOH) 292, 283, 273, and 268 nm; mass *m/e* 303 (M^+), 288, 170, 160, 143, and 133; NMR ($CDCl_3$) δ 2.53 (3 H, s, NCH_3), 5.90 (1 H, s, C3-H), 7.3–7.8 (8 H, m, ArH), and 8.2 (1 H, s, NH).

Anal. ($C_{19}H_{17}N_3O \cdot H_2O$) C, H, N.

Rutecarpine (3). A solution of 260 mg of 3,4-dihydro-β-carboline (**4**) in 15 ml of dry benzene was added to the sulfinamide anhydride **10** [prepared from 230 mg of anthranilic acid (**7**)] and the mixture was worked up as above to give 345 mg (80%) of rutecarpine (**3**) as pale yellow needles after recrystallization from ethyl acetate: mp 259 °C [lit.[13] mp 258 °C]; ir (KBr) 3325 (NH) and 1655 cm^{-1} (C=O); uv (MeOH) 360, 344, 330, 288, and 276 nm; mass *m/e* 287 (M^+), 259, 243, and 144; NMR ($CDCl_3$) δ 3.23 (2 H, t, J = 7 Hz, $ArCH_2$), 4.60 (2 H, t, J = 7 Hz, CH_2N), 7.3–7.8 (8 H, m, ArH), and 8.3 (1 H, s, NH).

Anal. ($C_{18}H_{13}N_3O$) C, H, N.

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Biomimetic Polyene Cyclizations.[1a,b,c] Asymmetric Induction in the Cyclization of a Dienic Acetal[1d]

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Abstract: Cyclization of the optically active acetal **1**, derived from the aldehyde **14** and (−)-2,3-butanediol, was studied to determine if the reaction proceeds with asymmetric induction. The aldehyde **14** was synthesized from the *trans*-bromodiene **9** by the sequence: **9** → **10** → **11** → **13** → **14.** Cyclization of acetal **1** with stannic chloride in benzene gave the axial hydroxy ether **15a,15b** and the epimeric equatorial hydroxy ether **16a,16b** as the major products. Cleavage of the side chain from each epimer (e.g., **15a,15b** → **17a,17b** → **5a,5b**) followed by oxidation gave the octalone **7a,7b.** The axially derived octalone **7a,7b** was converted to the hydrindanone **22** (i.e., **5a,5b** → **7a,7b** → **19** → **21** → **22**) and its ORD curve compared with the ORD curve from a sample of enantiomerically pure (+)-hydrindanone **22** of known absolute configuration. It was thus determined that the axially derived octalone consisted of 8% **7a** and 92% **7b,** and the equatorially derived octalone consisted of 92% **7a** and 8% of **7b.** An ORD value of $[\Phi]_{222}$ +11 180° was established for the pure octalone **7b,** which was used to calculate the enantiomeric ratios of various octalone specimens produced under different cyclization conditions. When the cyclization of **1** was conducted with stannic chloride in ultradry pentane or in nitromethane, the major products **15a,15b** and **16a,16b** were also formed with a high but lesser degree of asymmetric induction.

For several years our laboratories have been engaged in a study to test the hypothesis that the stereochemical course of squalene biocyclization may be controlled, at least in part, by stereoelectronic factors rather than by enzymic conformational influences.[3] We have, for example, demonstrated that appropriately constructed polyolefinic acetals undergo nonenzymic, acid-catalyzed cyclizations to give polycyclic substances possessing "natural" configuration.[1a,b,c,4] These cyclizations were stereospecific with respect to the relative configurations of the chiral centers produced at the bridgeheads; however, the products were racemic. In view of the fact that the enzymatic cyclization of squalene proceeds with total asymmetric induction to produce enantiomerically pure products, it has been our aim to simulate this process, at least qualitatively, in nonenzymic systems. To this end we decided to examine the cyclization of the optically active dienic acetal **1,** and we were gratified to find that the reaction did indeed proceed with a remarkably high degree of asymmetric induction without the agency of an enzyme. The present paper constitutes a detailed account of this study.

Previous work has shown that the cyclization of the *trans*-dienic acetal **2** proceeds in high yield and essentially stereospecifically with respect to the ring fusion.[1b] Thus when acetal **2** was treated with 5.0 molar equiv of stannic chloride in nitromethane at 0 °C for 3 min, an 80% yield of the racemic mixture **3a,3b** having an axial side chain at C-5 was obtained, along with 10% of the racemic mixture **4a,4b** having the epimeric equatorial side chain. Degradation of the side chain to