Iminoketene Cycloaddition. 2.[1] Total Syntheses of Arborine, Glycosminine, and Rutecarpine by Condensation of Iminoketene with Amides

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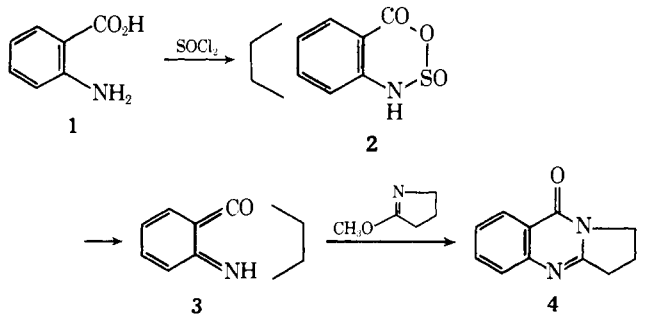
Abstract: Treatment of the sulfinamide anhydride **2**, derived from anthranilic acid (**1**), with primary and secondary amides gave the corresponding quinazolin-4-ones, the reaction of which was applied to one-step synthesis of quinazoline alkaloids, 6,7,8,9-tetrahydropyrido[2,1-*b*]quinazolin-11-one (**11**), glycosminine (**18**), and arborine (**21**). This paper also reports a total synthesis of rutecarpine (**28**) from **2** and *N*-formyltryptamine (**26**) via 3-indolylethylquinazolin-4-one (**27**).

Previously we have developed a new and one-step synthesis of quinazolone system **4** by a cycloaddition of the iminoketene **3**, generated in situ from anthranilic acid (**1**) via the sulfinamide anhydride (**2**), to imines (Scheme I), and this reaction has been applied to a total synthesis of evodiamine and rutecarpine along retro mass-spectral synthesis.[1] Although we have proposed a concerted reaction mechanism in this type of cycloaddition reaction,[1] a stepwise mechanism is likely. If the latter mechanism would contribute, the formation of quinazolines from the reaction of the iminoketene **3** with amides would be possible. Based on this premise, we have investigated the reaction of the sulfinamide anhydride **2** with several amides and here we wish to report our successful results.

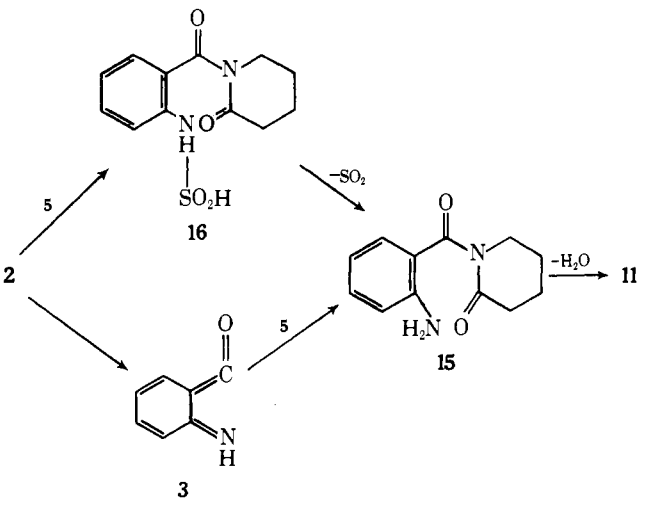
Scheme I



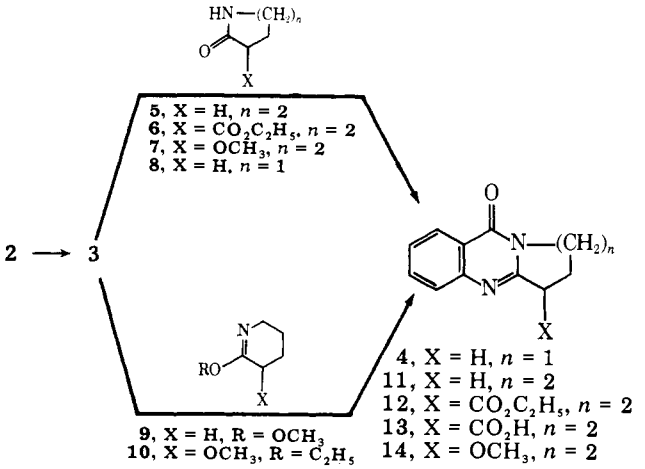
Firstly, the sulfinamide anhydride **2**, prepared from anthranilic acid (**1**) and thionyl chloride, was treated with 2-piperidone (**5**) (Scheme II) in dry benzene at room temperature overnight to give the condensation product, mp 99 ~ 99.5 °C, in 90% yield, whose IR [ν_{max} ($CHCl_3$) 1657 cm^{-1}] and NMR [δ ($CDCl_3$) 3.90 ~ 4.20 (2 H, t, J = 6 Hz) and 2.80 ~ 3.15 (2 H, t, J = 6 Hz)] spectra indicated this product to be 6,7,8,9-tetrahydropyrido[2,1-*b*]quinazolin-11-one (**11**). This structure was proved by direct comparisons with the authentic sample, prepared in 82.4% yield by our method[1] from the sulfinamide anhydride **2** and *O*-methylpiperidone (**9**), by melting point (lit.[2] mp 98.5 ~ 99.5 °C) and spectral comparisons. Thus we have developed a convenient synthesis of a quinazolone from anthranilic acid and an amide and also achieved a simple total synthesis of an alkaloid (**11**) from *Mackinlaya* species isolated by Fitzgerald et al.[2]

This reaction could proceed stepwise via an intermediate **15** (Scheme III) which formed through the intermediate **16** or by a condensation of the lactam **5** with the iminoketene **3**, generated in situ from the sulfinamide anhydride **2**.

Scheme III



Scheme II



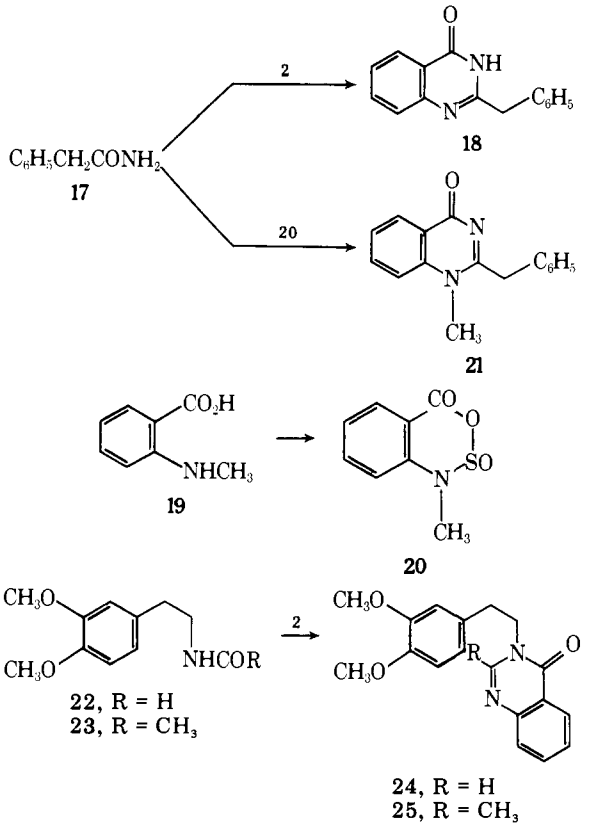
The reaction of **2** with the lactam ester **6**, which has two reaction sites, proceeded only in amide function to give the quinazolone-6-carboxylate **12**, mp 110 ~ 112 °C, in 95% yield. This product was converted into the quinazolone **11** by mild hydrolysis with 5% ethanolic sodium hydroxide, followed by decarboxylation of the resulting carboxylic acid **13** at 170 ~ 180 °C.

Similarly, 3-methoxypiperidone (**7**) reacted with the sulfinamide anhydride **2** in dry benzene at room temperature to form 6,7,8,9-tetrahydro-6-methoxypyrido[2,1-*b*]quinazolin-11-one (**14**) in 83% yield, which was also prepared in 70.6% yield by cycloaddition of **2** to the imine **10**.

The fact that the reaction of the lactams **5** and **7** with **2** proceeded in higher yield than that of the lactim ethers **9** and **10** as shown in the above examples indicates that this new synthesis of quinazolones is an effective method. Moreover, deoxyvasicinone (**4**)[1] was also obtained in 93% yield from pyrrolidone **8**, but the yield in a synthesis of **4** from the corresponding lactim ether was 64.5%.[1]

Secondly, we investigated the condensation of a noncyclic amide with the sulfinamide anhydride **2** on the grounds of the above finding. Thus, treatment of phenylacetamide (**17**) with sulfinamide anhydride **2** in dry benzene at room temperature gave, in 39.5% yield, 2-benzylquinazolin-4-one (**18**) (Scheme IV), *m/e* 236 (M^+), which was identical with glycosminine

Scheme IV

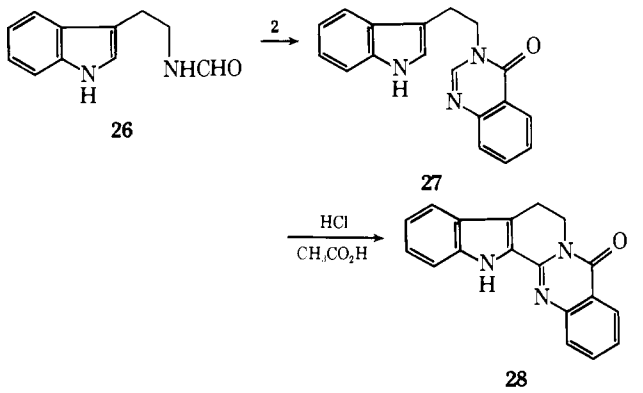


found in *Glycosmis arborea* as a minor alkaloid.[3] By the same method, arborine (**21**), an alkaloid from *G. arborea*,[4] was also synthesized in 54.5% yield by a condensation of **17** with the *N*-methylsulfinamide anhydride **20**,[1] prepared from *N*-methylanthranilic acid (**19**), in dry chloroform, and physical data of our product were identical with reported ones.[3,4]

N-Phenethylformamide (**22**) and *N*-phenethylacetamide (**23**) also reacted with the sulfinamide anhydride **2** in dry benzene to afford the corresponding 3-phenethylquinazolin-4-ones **24** and **25** 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 (**28**) (Scheme V), an alkaloid isolated from the fruit of *Evodia rutecarpa*,[5] by this method. A condensation of *N*-formyltryptamine (**26**) with the sulfinamide anhydride (**2**) 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 (**27**), mp 164 ~ 165 °C [*m/e* 289 (M^+); ν_{max} ($CHCl_3$) 3480 (NH) and 1660 cm^{-1} (CO); δ ($CDCl_3$) 6.75 (s, C_2-H)]. This product was heated with concentrated hydrochloric acid in acetic acid[6] at 110 °C for 166 h to afford rutecarpine (**28**), mp 259 °C, in 45% yield, whose IR, UV, and NMR spectra were superimposable upon those of the authentic sample.[1]

Scheme V



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

Experimental Section

Melting points are uncorrected. NMR spectra were taken with a JNM-PMX-60 spectrometer (tetramethylsilane as an internal reference), IR spectra with a Hitachi 215 spectrophotometer, UV spectra with a Hitachi 124 spectrophotometer, and mass spectra with a Hitachi RMU-7 spectrometer.

6-Ethoxycarbonyl - 6,7,8,9 - tetrahydropyrido[2,1-*b*]quinazolin-11-one (12). A solution of 100 mg of anthranilic acid (**1**) and 500 mg of thionyl chloride in 5 mL of dry benzene was refluxed for 2 h. The solvent was then evaporated under reduced pressure at 25 °C to afford sulfinamide anhydride **2** as an oily yellow liquid, to which a solution of 124 mg of 3-ethoxycarbonyl-2-piperidone (**6**) in 30 mL of dry benzene was added. After setting aside overnight at room temperature, the resulting mixture was washed with 10% aqueous potassium carbonate solution and water, dried over potassium carbonate, and evaporated. The residue was recrystallized from chloroform–hexane to yield 188 mg (95%) of 6-ethoxycarbonyl-6,7,8,9 - tetrahydropyrido[2,1-*b*]quinazolin-11-one (**12**) as yellow plates: mp 110 ~ 112 °C; IR ($CHCl_3$) 1670 ($CO_2CH_2CH_3$) and 1622 cm^{-1} (>NCO–); NMR ($CDCl_3$) δ 1.30 (3 H, t, J = 7 Hz, OCH_2CH_3), 1.59 ~ 2.20 (2 H, m, 8-H_2), 2.20 ~ 2.70 (2 H, m, 7-H_2), 3.7 ~ 4.15 (3 H, m, 6-H and 9-H_2), 4.23 (2 H, q, J = 7 Hz, OCH_2CH_3), 6.70 ~ 7.80 (3 H, m, 3 × ArH), and 7.95 ppm (1 H, d, J = 8 Hz, 1-H). Anal. ($C_{15}H_{16}N_2O_3$) C, H, N.

6,7,8,9 - Tetrahydropyrido[2,1-*b*]quinazolin-11-one (11). (a) From Sulfinamide Anhydride 2 and *O*-Methyllactim 9. To the sulfinamide anhydride **2**, prepared from 100 mg of anthranilic acid (**1**) as above, was added a solution of 82 mg of *O*-methyllactim **9** in 20 mL of dry benzene. After setting aside overnight at room temperature, the resulting mixture was worked up as above to give 120 mg (82.4%) of 6,7,8,9-tetrahydropyrido[2,1-*b*]quinazolin-11-one (**11**) as long colorless plates: mp 99 ~ 99.5 °C (lit.[2] 98.5 ~ 99.5 °C) (from ether–hexane); IR ($CHCl_3$) 1657 cm^{-1} (C=O); NMR ($CDCl_3$) δ 8.20 (1 H, q, J = 2 and 8 Hz, 1-H), 7.10 ~ 7.90 (3 H, m, 3 × ArH), 3.90 ~ 4.20 (2 H, t, J = 6 Hz, 9-H_2), 2.80 ~ 3.15 (2 H, t, J = 6 Hz, 6-H_2), and 1.70 ~ 2.30 (4 H, m, 7- and 8-H_2).

(b) From Sulfinamide Anhydride 2 and 2-Piperidone 5. To the sulfinamide anhydride **2**, obtained from 100 mg of anthranilic acid (**1**), was added a solution of 72 mg of 2-piperidone **5** in 10 mL of dry benzene. After setting aside overnight at room temperature, the reaction mixture was worked up as above to give 131 mg (90%) of **11**, whose melting point and IR and NMR spectral data are identical with those of the above compound.

(c) From 6-Ethoxycarbonyl-6,7,8,9-tetrahydropyrido[2,1-*b*]-quinazolin-11-one (12). A solution of 100 mg of **12** in 20 mL of 5% ethanolic sodium hydroxide solution was allowed to stand overnight at room temperature. The solvent was evaporated off under reduced pressure to afford a residue, to which was added an excess of acetic acid. After evaporation of acetic acid, the residue was heated at 170 ~ 180 °C for 2 h, then dissolved in 10% aqueous potassium carbonate solution, and extracted with chloroform. The chloroform layer was washed with water, dried over potassium carbonate, and evaporated. Recrystallization from ether–hexane gave 69 mg (94%) of **11**, whose

Table I. Elemental Analysis Data

Compd	Formula	Found, %			Calcd, %		
		C	H	N	C	H	N
12	$C_{15}H_{16}N_2O_3$	66.21	5.77	10.19	66.16	5.92	10.29
14	$C_{13}H_{14}N_2O_2$	67.34	6.03	12.41	67.81	6.13	12.17
24	$C_{18}H_{18}N_2O_3$	70.02	6.00	9.29	69.66	5.85	9.03
25	$C_{19}H_{20}N_2O_3$	70.48	6.35	8.35	70.35	6.22	8.64
27	$C_{18}H_{15}N_3O \cdot 0.66H_2O$	71.73	5.38	13.38	71.57	4.99	13.88

melting point and IR and NMR spectral data are identical with those of the above product.

Deoxyvasicinone (4). To the sulfinamide anhydride **2,** obtained from 50 mg of anthranilic acid (**1**), was added a solution of 31 mg of 2-pyrrolidone (**8**) in 20 mL of dry benzene. The resulting mixture was set aside overnight at room temperature and then worked up as in the case of **12** to afford 63 mg (93%) of deoxyvasicinone (**4**) as colorless needles, mp 196 ~ 198 °C (lit.[1] mp 196 ~ 198 °C) (from chloroform–hexane), whose spectral data and TLC behaviors in various solvent systems were identical with those of the authentic sample.[1]

6,7,8,9 - Tetrahydro-6-methoxypyrido[2,1 - *b*]quinazolin-11-one (14). (a) To the sulfinamide anhydride **2,** obtained from 300 mg of anthranilic acid (**1**) in a usual manner as above, was added a solution of 300 mg of 2-ethoxy-3,4,5,6-tetrahydro-3-methoxypyridine (**10**) in 15 mL of dry benzene. After setting aside for 2 h at room temperature, the mixture was evaporated to give a residue, which was partitioned between chloroform and 5% aqueous sodium hydroxide solution. The chloroform layer was washed with water, dried over anhydrous sodium sulfate, and evaporated to yield 500 mg of a brown syrup, which was purified by column chromatography on 10 g of silica gel. Elution with benzene gave 310 mg of **14** (70.6%) as a yellow syrup: IR ($CHCl_3$) 1660 cm^{-1} (C=O); NMR ($CDCl_3$) δ 2.00 (4 H, m, $NCH_2CH_2CH_2$), 3.40 (3 H, s, OCH_3), 4.10 (3 H, m, NCH_2 and 6-H), and 7.30 ~ 8.20 (4 H, m, 4 × ArH); mass spectrum *m/e* 230 (M^+). Anal. ($C_{13}H_{14}N_2O_2$) C, H, N.

(b) To the sulfinamide anhydride **2,** prepared from 1.0 g of anthranilic acid (**1**), was added a solution of 900 mg of 3-methoxy-2-piperidone (**7**) in 30 mL of dry benzene. The resulting mixture was set aside for 2 h at room temperature and worked up as above to yield 1.5 g (83.3%) of **14** as a yellow syrup, whose IR, NMR, and mass spectra were identical with those of the above sample.

3-(6,7 - Dimethoxyphenethyl) -3,4- dihydroquinazolin-4-one (24). To the sulfinamide anhydride **2,** prepared from 100 mg of anthranilic acid (**1**), was added a solution of the amide **22** in 40 mL of dry benzene. The resulting mixture was set aside overnight at room temperature. The precipitated crystals were collected by filtration, dissolved in 5% sodium hydroxide solution, and extracted with chloroform. The chloroform layer was washed with water and dried over potassium carbonate. After evaporation of the solvent, the residue was recrystallized from chloroform–hexane to afford 200 mg (89%) of 3-(6,7-dimethoxyphenethyl)-3,4-dihydroquinazolin-4-one (**24**) as colorless crystals: mp 107 ~ 109 °C; IR ($CHCl_3$) 1665 cm^{-1} (C=O); NMR ($CDCl_3$) δ 3.08 (2 H, t, J = 6.8 Hz, $PhCH_2CH_2$), 3.78 (3 H, s, OCH_3), 3.82 (3 H, s, OCH_3), 4.20 (2 H, t, J = 6.8 Hz, $PhCH_2CH_2$), 6.50 ~ 6.90 (3 H, m, 3 × ArH), 7.40 ~ 7.90 (4 H, br s, 3 × ArH and N–CH=N), and 8.32 ppm (1 H, d, J = 8 Hz, 5-H); mass spectrum *m/e* 310 (M^+). Anal. ($C_{18}H_{18}N_2O_3$) C, H, N.

3-(6,7-Dimethoxyphenethyl) -3,4 -dihydro-2-methylquinazolin-4-one (25). To the sulfinamide anhydride **2,** prepared from 100 mg of anthranilic acid (**1**), was added a solution of 162 mg of the amide **23** in 20 mL of dry benzene. The resulting mixture was set aside overnight at room temperature. The precipitated crystals were collected by filtration, dissolved in 5% aqueous sodium hydroxide solution, and extracted with chloroform. The chloroform layer was washed with water and dried over potassium carbonate. After evaporation of the solvent, the residue was recrystallized from ethanol–ether to yield 199 mg (84%) of 3-(6,7-dimethoxyphenethyl)-3,4-dihydro-2-methylquinazolin-4-one (**25**) as yellow crystals: mp 103 ~ 104 °C; IR ($CHCl_3$) 1660 cm^{-1} (C=O); NMR ($CDCl_3$) δ 2.45 (3 H, s, N=C–CH_3), 2.99 (2 H, t, J = 7 Hz, $PhCH_2CH_2$), 3.65 (3 H, s, OCH_3), 3.83 (3 H, s, OCH_3), 4.26 (2 H, t, J = 7 Hz, $PhCH_2CH_2$), 6.60 ~ 6.83 (3 H, m, 3 × ArH), 7.30 ~ 7.90 (3 H, m, 3 × ArH), and 8.23 ppm (1 H, d, J = 8 Hz, 5-H). Anal. ($C_{19}H_{20}N_2O_3$) C, H, N.

Glycosminine (18). To the sulfinamide anhydride **2,** obtained from 100 mg of anthranilic acid (**1**), was added a solution of 98 mg of phenylacetamide (**17**) in 200 mL of dry benzene. The resulting mixture was set aside overnight at room temperature. The precipitated crystals were collected by filtration and identified as recovered phenylacetamide. The mother liquor was then evaporated under reduced pressure to yield a residue which was treated with a mixture of chloroform–5% aqueous sodium hydroxide solution under vigorous stirring in order to hydrolyze the known dimer[7] resulting from the intermediate iminoketene. After dilution with chloroform, the chloroform layer was washed with water, dried over potassium carbonate, and evaporated under reduced pressure to afford 68 mg (39.5%) of glycosminine (**18**) as fine crystals: mp 247 ~ 249 °C (lit.[3] mp 249 °C); IR ($CHCl_3$) 1670 cm^{-1} (C=O); NMR ($CDCl_3$) 4.10 (2 H, s, $PhCH_2$), 7.10 ~ 7.80 (8 H, m, 8 × ArH), and 8.26 (1 H, d, J = 8 Hz, 5-H); mass spectrum *m/e* 236 (M^+).

Arborine (21). To the sulfinamide anhydride **20,** prepared from 100 mg of *N*-methylanthranilic acid (**19**), was added a solution of 89 mg of phenylacetamide (**17**) in 300 mL of dry chloroform. The resulting mixture was set aside at room temperature, washed with 10% aqueous potassium carbonate solution and water, and dried over potassium carbonate. After evaporation of the solvent, the residue was submitted to silica gel column chromatography with benzene as eluent to yield 90 mg (54.5%) of arborine (**21**), mp 154 ~ 156 °C (lit.[3] 155 ~ 156 °C), whose IR, NMR, and mass spectral data were identical with those of the natural product:[4] IR ($CHCl_3$) 1640 cm^{-1} (C=O); NMR ($CDCl_3$) δ 3.60 (3 H, s, NCH_3), 4.26 (2 H, s, $PhCH_2$), 7.10 ~ 7.90 (8 H, m, 8 × ArH), and 8.30 (1 H, q, J = 8 and 2 Hz, 5-H); mass spectrum *m/e* 250, 249, 133, 132, 105, and 104.

3-Indolylethylquinazolin-4-one (27). To the sulfinamide anhydride **2,** prepared from 150 mg of anthranilic acid (**1**), was added a solution of 200 mg of *N*-formyltryptamine (**26**) in 10 mL of benzene and 10 mL of chloroform. After being allowed to stand for 2 h at room temperature, the mixture was evaporated to give a residue, which was partitioned between chloroform and 5% aqueous sodium hydroxide solution. The chloroform extract was washed with water, dried over sodium sulfate, and evaporated to afford 250 mg of an orange syrup, which was chromatographed on 5.0 g of silica gel. Elution with benzene–ethyl acetate (9:1 v/v) gave a solid, which was recrystallized from ethyl acetate–hexane to yield 200 mg (62.9%) of 3-indolylethylquinazolin-4-one (**27**) as colorless crystals: mp 164 ~ 165 °C; IR ($CHCl_3$) 3480 (NH) and 1660 cm^{-1} (C=O); NMR ($CDCl_3$) δ 3.25 (2 H, t, J = 7 Hz, CH_2CH_2N), 4.25 (2 H, t, J = 7 Hz, CH_2CH_2N), 6.75 (1 H, broad s, indole α-H), 7.0 ~ 7.7 (8 H, m, 7 × ArH and >NC*H*=N-), and 8.20 (1 H, q, J = 2 and 8 Hz, 5-H); mass spectrum *m/e* 289 (M^+). Anal. $C_{18}H_{15}N_3O \cdot 0.66H_2O$ C, H, N.

Rutecarpine (28). A mixture of 200 mg of the above quinazolin-4-one **27,** 7 mL of concentrated hydrochloric acid, and 7 mL of glacial acetic acid was heated for 166 h at 110 °C with stirring. To the above mixture 10% aqueous sodium hydroxide solution was slowly added in order to basify the reaction mixture, which was extracted with chloroform. The chloroform layer was washed with water, dried over sodium sulfate, and evaporated to give 120 mg of a colorless powder, which was subjected to silica gel column chromatography. The elution with benzene–ethyl acetate (8:2 v/v) gave 100 mg of a colorless powder, which was recrystallized from ethyl acetate to yield 85 mg (42.5%) of rutecarpine (**28**) as colorless needles, mp 259 °C (lit.[1] 259 °C), whose IR, UV, and NMR spectra were identical with those of the authentic sample.[1]

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Synthesis of Cycloheptaamylose 2-, 3-, and 6-Phosphoric Acids, and a Comparative Study of Their Effectiveness as General Acid or General Base Catalysts with Bound Substrates[1]

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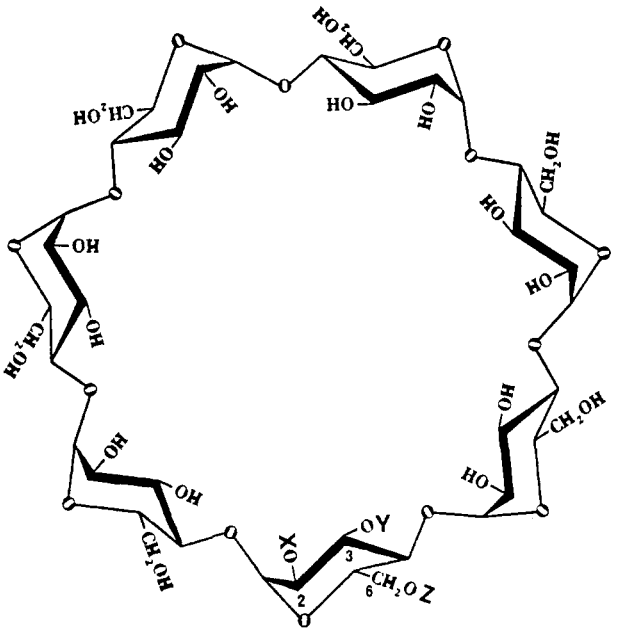
Abstract: The title compounds were prepared and examined as catalysts for the hydrolysis of *p*-nitrophenyl tetrahydropyranyl ether at low pH and the exchange of *p-tert*-butylphenacyl alcohol tritiated in the methylene group at high pH. All three isomers, as the phosphate dianions, were effective catalysts for the latter reaction, in which the functional group assists enolization of the bound ketone. Only the 3-phosphoric acid isomer showed net catalysis of the former reaction, bound substrate being hydrolyzed with the assistance of a monoanion phosphoric acid group.

The cyclodextrins (cycloamyloses) are of interest in the construction of enzyme models because they have a hydrophobic cavity of a size convenient to bind organic molecules and groups.[2] A number of reactions have been observed in which, in aqueous solutions, a cyclodextrin binds a substrate molecule into its hydrophobic interior and then catalyzes an interaction with one of the hydroxyl groups which rim the cyclodextrin cavity.[3] In addition, several kinds of functional group changes have been performed on cyclodextrin which make it even more interesting in the construction of artificial enzymes. For instance, the cavity has been modified in such a way as to provide it with a hydrophobic floor[4] to give improved binding and catalytic properties for some reactions. More generally, a multitude of functional groups have been attached to the secondary (carbons 2 and 3) and primary (carbon 6) edge of the cyclodextrin molecules.[5] In this way various nucleophilic catalysts, and catalytic metal ions, have been employed in the catalytic reactions of substrates which are also bound in the hydrophobic cavity. We now wish to report the synthesis and characterization of the three monophosphates (**1**, **2**, and **3**) of β-cyclodextrin (cycloheptaamylose)[6] in which the phosphoric acid group is attached respectively to carbons 2, 3, and 6.

Phosphate groups can act as either general base or general acid catalysts, depending on the pH. We wanted to see whether such catalysis could be demonstrated with a substrate bound in the cavity. We also wanted to explore the relative catalytic effectiveness of the three isomers[7,8] to learn more about the optimal placement of a catalytic group relative to the cavity.

As the substrate for general acid catalysis we used *p*-nitrophenyl tetrahydropyranyl ether (**4**), a model of a simple glycoside. Fife has shown[9] that **4** can be hydrolyzed with general acid catalysis in mixed aqueous or water solvents, with a much faster rate in water. Since the cyclodextrin molecule is quite large, its immediate vicinity might well be only partially aqueous in character even in water solution.[10] In fact, we did observe general acid catalysis of the hydrolysis of **4**, but only with isomer **2**. Although these compounds are of interest as catalysts in their own right regardless of their relationship to any natural system, it should be noted that the enzyme phosphorylase apparently also uses a phosphate group (attached to bound pyridoxal) as a catalyst in glycoside cleavage.[11]



1, X = PO_3H_2, Y = Z = H
2, Y = PO_3H_2, X = Z = H
3, Z = PO_3H_2, X = Y = H
7, Z = $PO_3(C_6H_5)_2$, X = Y = H