(1.42 mL) was stirred at 0 °C for 1.5 h. After addition of brine (2 mL), the mixture was extracted with ethyl acetate (3 × 3 mL). The combined organic extracts were washed with brine, dried, and evaporated. The residue was purified by chromatography to yield **23** (57 mg, 65%) as an oil: $[\alpha]^{25}_D$ -2.29° (*c* 1.245, $CHCl_3$); IR (neat) 3460, 1720, 1710, 1660 cm^{-1}; ^1H NMR ($CdCl_3$) δ 1.46 (s, 9 H), 2.38-2.42 (m, 2 H), 2.99 (br s, 1 H), 3.72 (s, 3 H), 3.58-3.76 (m, 2 H), 3.82-4.07 (m, 2 H), 5.41 (d, *J* = 9.0 Hz, 1 H), 5.92 (d, *J* = 16 Hz, 1 H), 6.96-7.05 (m, 1 H); HRMS calcd for $C_{13}H_{23}NO_6$ 289.1526, found 289.1559.

Methyl *N*-(*tert*-Butoxycarbonyl)galantinate (24) and the C-3 Epimer 25. A mixture of **23** (21.4 mg, 0.074 mmol) and K_2CO_3 (0.51 mg, 0.0037 mmol) in MeOH (0.2 mL) was stirred at room temperature for 20 h. After evaporation of the solvent, the residue was chromatographed to yield **24** (5.4 mg, 25%) and **25** (6.1 mg, 29%).

24: mp 106-106.5 °C; $[\alpha]^{25}_D$ -5.7° (*c* 0.19, $CHCl_3$) [lit[19b] $[\alpha]^{24}_D$ -5.4° (*c* 0.8, $CHCl_3$), mp 104.5-106 °C]; IR (KBr) 3457, 3404, 1734, 1678 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41-1.47 (m, 1 H), 1.44 (s, 9 H), 2.10 (ddd, *J* = 1.95, 4.64, 12.09 Hz, 1 H), 2.45 (dd, *J* = 5.19, 15.6 Hz, 1 H), 2.60 (dd, *J* = 7.93, 15.6 Hz, 1 H), 3.09 (dd, $J_1 = J_2$ = 11.0 Hz, 1 H), 3.40-3.51 (m, 1 H), 3.51-3.62 (m, 1 H), 3.70 (s, 3 H), 3.76-3.86 (m, 1 H), 4.01 (dd, *J* = 4.88, 11.3 Hz, 1 H), 4.48 (br s, 1 H). Anal. Calcd for $C_{13}H_{23}NO_6$: C, 53.97; H, 8.01; N, 4.84. Found: C, 54.38; H, 8.03; N, 4.37.

25: oil; $[\alpha]^{25}_D$ +19.2° (*c* 0.31, MeOH), [lit.[19a] $[\alpha]^{26}_D$ +20.8° (*c* 1.5, MeOH)]; IR (neat) 3448, 1736, 1685 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (s, 9 H), 1.68-1.73 (m, 2 H), 2.39 (dd, *J* = 4.9, 15.1 Hz, 1 H), 2.50 (dd, *J* = 8.3, 15.1 Hz, 1 H), 3.30-3.60 (m, 1 H), 3.67 (d, *J* = 12.0 Hz, 1 H), 3.70 (s, 3 H), 4.04-4.21 (m, 3 H), 5.18 (d, *J* = 7.8 Hz, 1 H); HRMS calcd for $C_{13}H_{23}NO_6$ 289.1526, found 289.1529.

Acknowledgment. We thank Dr. Y. Ohfune, Suntory Institute for Bioorganic Research, for informing us to the revised structure of galantin I.

Registry No. (±)-**1**, 108998-71-6; (3*R*)-**1**, 130192-96-0; (3*S*)-**1**, 130192-97-1; (3*S*,4*R*)-**2**, 130096-82-1; (3*R*,4*S*)-**2**, 130193-00-9; (2*S*,3*S*)-**3**, 130193-01-0; (2*R*,3*R*)-**3**, 130193-02-1; (2*S*,3*R*)-**5**, 130194-08-0; (2*R*,3*S*)-**5**, 130194-09-1; **6**, 130193-03-2; **7**, 123287-88-7; **9**, 130096-76-3; **10**, 89985-84-2; **11**, 90011-42-0; (2*S*,3*S*)-**12**, 130192-98-2; (2*R*,3*R*)-**12**, 123287-87-6; **13**, 130096-77-4; **15**, 130120-89-7; **16**, 130096-78-5; **17**, 127852-65-7; **18**, 120409-91-8; (4*S*,5*S*)-**19**, 130192-99-3; (4*R*,5*R*)-**19**, 123163-94-0; **20**, 130096-79-6; **21**, 130096-80-9; **22**, 130096-81-0; **23**, 129397-16-6; **24**, 89985-68-2; **25**, 92143-26-5; AcOBu-*t*, 540-88-5; 4-BrC_6H_4OMe, 104-92-7; Ph_3P=CHCOOMe, 2605-67-6; (-)-detoxinine, 54963-44-9; (-)-anisomycin, 22862-76-6; (+)-galantinic acid, 78330-63-9; (3*S*,3*R*)-3-hydroxyglutamic acid, 6208-98-6.

Investigations into a Mild Diels-Alder Approach to 6-Substituted Quinazoline-2,4-dione Derivatives

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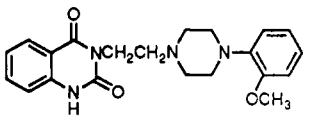
Furo[3,4-*d*]pyrimidine-2,4-dione (**2**) has been reacted with a number of dienophiles to give the Diels-Alder adducts such as **3** and **4** under very mild reaction conditions. Methyl acrylate gives only two regioisomeric endo products which have been isolated and characterized. Other dienophiles give mixtures of endo and exo products as well as of regioisomers. The product ratios were determined by high field ^1H NMR analysis. These adducts are dehydrated by treatment with acid to form some novel quinazoline-2,4-dione derivatives.

During the course of our work investigating the potent antihypertensive quinazoline-2,4-dione **1** (SGB 1534),[1] we prepared the furan isostere **2a**[2] as well as the thiophene isostere **2b**.[3] Investigation of the structure-activity relationships in these series of compounds led us to study N-substitution of furo[3,4-*d*]pyrimidinedione **2a** and we discovered an interesting Diels-Alder reaction which occurred in good yield under unusually mild conditions.



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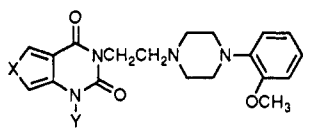
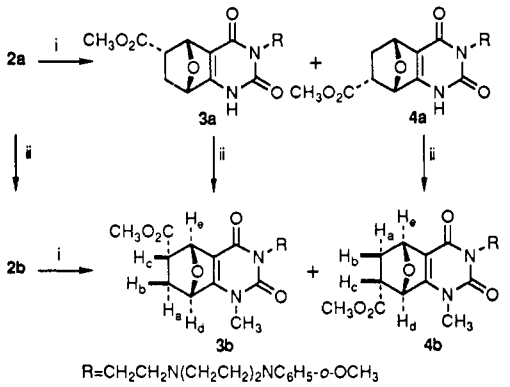


2a, X=O, Y=H
2b, X=S, Y=H
2c, X=O, Y=CH_3

In general, *N*1-alkyl derivatives may be prepared in the expected way by treatment of furo[3,4-*d*]pyrimidine-2,4-dione **2a** with sodium hydride and the appropriate alkyl halide in DMF at 0 °C to room temperature. However, when methyl 3-bromopropionate is used as the alkylating agent, no *N*-alkyl derivative was isolated, which is in sharp contrast to the analogous reaction for thiophene **2b**.[3] Instead, a mixture of two products is formed which was

Scheme I[a]



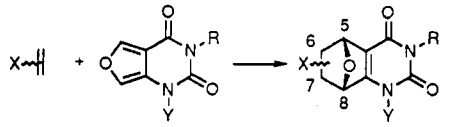
R=$CH_2CH_2N(CH_2CH_2)_2NC_6H_5$-*o*-$OCH_3$

[a] (i) Methyl 3-bromopropionate/NaH/DMF or methyl acrylate, DMF, room temperature. (ii) NaH, CH_3I, DMF, room temperature.

(1) Nagano, H.; et al. Eur Pat. 89 065, 1983, Chugai Pharmaceutical Co., Ltd.; *Chem. Abstr.* **1984**, *100*, 6547p.
(2) Press, J. B.; McNally, J. J.; Keiser, J. A.; Offord, S. J.; Katz, L. B.; Giardino, E.; Falotico, R.; Tobia, A. *Eur. J. Med. Chem.* **1989**, *24*, 627.
(3) Russell, R. K.; Press, J. B.; Rampulla, R. A.; McNally, J. J.; Falotico, R.; Keiser, J. A.; Bright, D. A.; Tobia, A. *J. Med. Chem.* **1988**, *31*, 1786.

0022-3263/91/1956-0245$02.50/0

Table I. Ratios and Yields of Diels–Alder Adducts of Furo[3,4-*d*]pyrimidine-2,4-diones



R=$CH_2CH_2N(CH_2CH_2)_2NC_6H_5$-*o*-$OCH_3$

			ratio[a]				
entry	X	Y	6-endo	6-exo	7-endo	7-exo	yield,[b] %
1	CO_2CH_3	H	4[c]	0	1[c]	0	85
2	CO_2CH_3	CH_3	2[c]	0	1	0	77
3	$COCH_3$	H	4[c]	trace	1	trace	86
4	$COCH_3$	CH_3	3[c]	trace	1	trace	81
5	CN	H	6	3	3	1	81
6	CN	CH_3	4	2	6	1	98
7	SO_2CH_3	H	3	–[d]	1	–[d]	46
8	SO_2CH_3	CH_3	1	trace	1	trace	74

entry	X	Y	endo:exo	yield, %
9	6,7-$(CO_2CH_3)_2$	H	10[c]:1	74
10	6,7-$(CO_2CH_3)_2$	CH_3	10:1	69
11	H	H	–	40

[a] Ratios are determined by ^{1}H NMR analysis of the crude reaction mixture by comparison of integrals. [b] Overall yields are the result of 1–3 experiments and have not been maximized. [c] Products isolated and completely characterized. [d] Exo products are present by ^{1}H NMR analysis. Relative ratios could not be determined as a consequence of proton absorption overlap. Combined yields of exo products ≈20%.

assigned as Diels–Alder adducts **3a** and **4a** by ^{1}H NMR analysis (Scheme I). These 5,8-epoxy-5,6,7,8-tetrahydro-1*H*-quinazoline-2,4-diones (**3a** and **4a**) may be separated by flash chromatography and subsequent medium-pressure chromatography and completely characterized by ^{1}H NMR, IR, MS, and combustion analyses. Methyl 3-bromopropionate is not required since treatment of **2a** with methyl acrylate without base for several hours at room temperature gives the same result. The *N*-methylfuro[3,4-*d*]pyrimidinedione (**2c**) undegoes the Diels–Alder reaction equally well to give adducts **3b** and **4b**. This result demonstrates that there is essentially no anionic assistance to facilitate this mild Diels–Alder chemistry. For complete structural correlation, **3a** and **4a** were readily converted to the corresponding *N*-methyl derivatives **3b** and **4b**, respectively, using sodium hydride and methyl iodide in DMF.

Stereo- and regiochemistry of *N*-methyl derivatives **3b** and **4b** were deduced by ^{1}H NMR analysis. The signals for the bridgehead protons H_d and H_e are assigned by characteristic chemical shifts and appear as a pair of doublets for each isomer. The expected coupling of bridgehead protons and adjacent endo protons is essentially zero in systems related to norbornane.[4] Since both bridgehead protons of both **3b** and **4b** appear as doublets, both the methylene and methyne carbons must bear an exo proton and, as a consequence, the carbomethoxyl group must occupy an endo position. This product formation is in accordance with the "endo rule" predicted with product formation arising from a concerted, kinetically controlled Diels–Alder reaction. The regiochemistry of **4b** was derived from a nuclear Overhauser effect (NOE) seen on bridgehead proton H_d, peri to the *N*-methyl group, upon irradiation of the *N*-methyl absorption. A COSY experiment shows that H_d is coupled to H_c, the proton α to the carbomethoxyl group (H_c). Similar experiments were used to establish the regiochemistry of **3b**.

Using the stereo- and the regiochemistry thus established, analysis of reaction mixtures using high-field ^{1}H NMR comparing the ratio of the integrals of the bridgehead protons, allows the determination of product ratios. The ratio of **3b**:**4b** is approximately 2:1 while the ratio of **3a**:**4a** is 4:1. This result is contrary to expectations where *N*-methyl derivatives should more favor the formation of **3b** for steric considerations. The regiochemistry may be crudely rationalized in terms of the enhanced electron density on the furan carbon α to the amine substitution and will be discussed further vide infra.

While, intermolecular Diels–Alder reactions of furans are well known, they usually require prolonged heating,[5] catalysts,[6] or high pressure.[7] The mild reaction conditions (≤room temperature, 1 equiv of dienophile, ≤16 h) prompted us to investigate the generality of the reaction. In addition, since Diels–Alder reaction products of furan may be dehydrated to benzene derivatives[5] and the reaction favors 6-substitution regiochemistry (generally difficult to achieve in quinazolinedione systems), we hoped to utilize this technology to prepare several novel quinazolinedione derivatives for further study.

Furans **2a** and **2c** react with a number of dienophiles (Table I). Olefins with a single electron withdrawing group (entries 1–8) are the best dienophiles and react at room temperature to give a mixture of Diels–Alder adducts in high yield. While methyl acrylate gives exclusively endo products (entries 1, 2), other olefins produce mixtures of endo and exo products to varying degrees (entries 3–10). The exo products, although never isolated, could be identified in the reaction mixture by ^{1}H NMR. For example, the exo Diels–Alder adducts of acrylonitrile (entries 5, 6) have bridgehead protons whose signals appear in the 5–6 ppm region as a doublet and a singlet; the singlet is the bridgehead proton adjacent to the methyne proton. Integrations of the signals for the bridgehead protons give the relative ratios of the Diels–Alder adducts.

Dimethyl maleate (entries 9, 10) reacts with furopyrimidinediones **2a** and **2c** but requires heat (80–100 °C)

(4) (a) Abraham, R. J.; Loftus, P. *Proton and Carbon-13 NMR Spectroscopy*; Heyden & Son Ltd.: Bristol, 1979; p 45. (b) Gordon, A. J.; Ford, R. A. *The Chemist's Companion*; Wiley: New York, 1972; p 274.

(5) Kunstmann, M. P.; Tarbell, S. D.; Autrey, R. L. *J. Am. Chem. Soc.* **1962**, *84*, 4115.

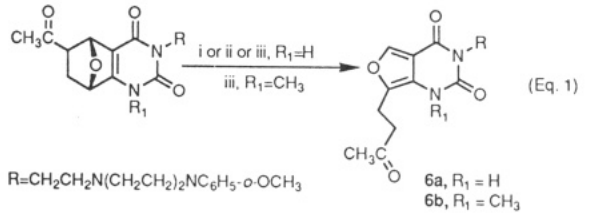
(6) Bion, F. *Tetrahedron Lett.* **1982**, *23*, 5299.

(7) Dauben, W. G.; Krabbenhoft, H. O. *J. Am. Chem. Soc.* **1976**, *98*, 1992.

to form endo and exo products in low to moderate yields. Even ethylene (entry 11), a notoriously poor dienophile, forms a Diels–Alder adduct with gentle heating. Of the solvents used (DMF, methylene chloride, methanol, tetrahydrofuran), DMF gives the best overall yields of adducts under the mildest reaction conditions. This result may be due to poor reactant solubility in several of these solvents.

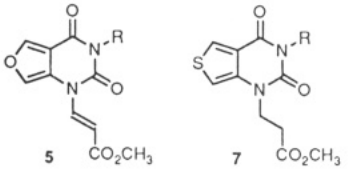
Other dienophiles do not give isolable products. When **2a** is treated with maleic anhydride, ^{1}H NMR shows a Diels–Alder adduct mixed with small amounts of **2a**, but only starting material **2a** is recovered in high yield from silica gel chromatography. Apparently, the maleic anhydride adduct readily undergoes retro-Diels–Alder reaction. 1,4-Benzoquinone and dimethyl acetylenedicarboxylate fail to react with **2a** at room temperature and cause decomposition at elevated temperatures. Methyl propiolate reacts with **2a** at room temperature to give the Michael addition product **5** rather than a Diels–Alder adduct. Benzyne (generated from anthranilic acid[8]) failed to react with **2a**.

While the Diels–Alder reactions occur very smoothly, attempts to purify many of the products on conventional or reverse-phase silica gel systems were frustrated by the poor resolution as well as the number of adducts. Attempts to selectively crystallize the adducts were equally futile. This is most likely an artifact of the (arylpiperazinyl)ethyl side chain required for our target compounds. In the case of the methyl vinyl ketone adducts (Table I, entries 3, 4), product isolation is also frustrated by a retro-Michael-type reaction to reform the furan system **6** (eq 1). Presumably, **6** arises by nitrogen facilitated

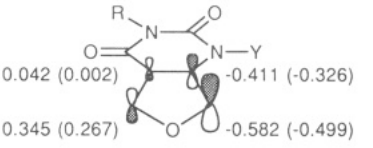


displacement of a carbonyl-activated methylene, proton transfer, and aromatization. While the generality of this rearrangement has not been explored, *N*-methyl substitution prevents this reaction under neutral conditions. The rearrangement does not occur for methyl acrylate adducts (Table I, entries 1, 2).

Not surprisingly, reexamination of the thiophene isostere **2b** shows it to be a poor diene for an analogous Diels–Alder reaction. When treated with methyl acrylate under identical conditions, the N-alkylated product **7**[3] is formed essentially exclusively in 99% yield. The *N*-methyl derivative of **2b** fails to react with methyl acrylate up to 100 °C.



The regiochemistry of the Diels–Alder reaction requires further discussion. As noted earlier, 6-substituted products such as **3a** or **3b** may arise by the directing influence of the nitrogen substituent on furan **2a** or **2c**. Molecular modeling considerations lead to a good prediction of the



MNDO values are for Y = H (Y = CH_3)

X	Φ	Φ
CO_2CH_3	0.460	-0.605
$COCH_3$	0.432	-0.629
CN	0.571	-0.696
SO_2CH_3	0.340	-0.059

Figure 1. MNDO coefficients for HOMO of furo[3,4-*d*]pyrimidine-2,4-dione and LUMO of various dienophiles.

observed regiochemistry in most cases. MNDO[9] coefficients were calculated (Figure 1) for the highest occupied molecular orbital (HOMO) of the dienes **2a** and **2c** and the lowest unoccupied molecular orbital (LUMO) of selected dienophiles. For methyl acrylate, the best overlap of molecular orbitals, based on the magnitudes of the absolute values of the calculated coefficients, predict 6-substituted **3a** and **3b** to be the major products. Methyl vinyl ketone has a similar overlap and gives similar results (Table I). In the case of acrylonitrile, similar regiochemical results are predicted and observed for the case of the N-H diene **2a**, but the predictivity diminishes for the *N*-methyl diene **2c**. Overlaps for the sulfone are poor for either orientation in either case, but there are reports that measured physical properties (especially heats of formation) of sulfones are not in good agreement with the predicted values based on MNDO calculations.[10]

The high levels of stereochemical control for these reactions are worthy of note. Previous reports considering frontier orbital theory suggest that regioselectivity (and, consequently, stereoselectivity) arises from secondary orbital interactions.[11a] In light of the extremely small dienyl C-3 HOMO coefficient (0.042 or 0.002), the origin of the large degree of endo selectivity for the majority of examples (Table I, entries 1–5, 8–10) is not apparent.[11b]

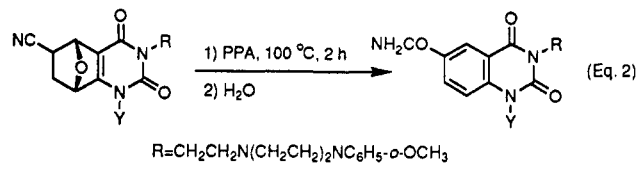
As a result of these studies, a number of 6- and 7-substituted 5,8-epoxy-5,6,7,8-tetrahydro-1*H*,3*H*-quinazoline-2,4-diones may be prepared. As discussed, we hoped to prepare the corresponding substituted quinazoline-2,4-diones from these derivatives. As may be seen in Table II, many of the Diels–Alder adducts in this study can be smoothly dehydrated to their corresponding quinazoline-2,4-diones by the action of sulfuric acid at room temperature or polyphosphoric acid at 120 °C in varying yields. For the 6-acetyl compounds (Table I, entries 3, 4), rearrangement to furan **6** occurs in concentrated sulfuric acid (as already discussed, eq 1) instead of dehydration. In the case of the cyanoquinazolines, dehydration in PPA and subsequent aqueous work up gives a carboxamide rather than the nitrile derivative (eq 2).[12] We believe that the

(8) Freidman, L.; Lugullo, F. M. *J. Org. Chem.* **1969**, *34*, 3089.

(9) MOPAC 5.00 was written by Stewart, J. J. P., U. S. Air Force Academy, Colorado Springs, Colorado 80840 and is available from QCPE.

(10) Stewart, J. J. P. *J. Comp. Chem.* **1989**, *10*, 221.

(11) (a) Fleming, I.; Michael, J. P.; Overman, L. E.; Taylor, G. F. *Tetrahedron Lett.* **1978**, 1313 and references contained therein. (b) A study of the origins of the high stereoselectivity of this reaction is underway and is the subject of a future report.



(Eq. 2)

yields for dehydration as shown in Table II are lower than might be anticipated as a consequence of the difficulty in product isolation of the basic piperazine-containing product from the acidic aqueous workup mixture. While we have not performed experiments wherein the N3 substituent (R) was a simple alkyl, aryl (or even hydrogen) since these derivatives were not germaine to our biological goals, we believe that such substitution would allow much easier product isolation with consequent increased yield. One other limitation in the scope of this approach to quinazoline synthesis is apparent from entries 9 and 10 (Table II) wherein the 6 and 7 isomers are difficult to separate. Clearly, in spite of these considerations, very acceptable yields of 6-substituted quinazolines (cf. entries 2 and 3) are possible.

Quinazoline-2,4-diones are generally prepared from isatoic anhydride precursors. Since 6-substituted isatoic anhydrides are not generally available, quinazoline-2,4-diones with electron-deficient 6-substituents are difficult to obtain. The Diels–Alder approach described herein occurs under remarkably mild reaction conditions and uses readily available furan derivatives. This reaction can give highly selective 6-substitution; our initial studies show some limitations of the regioselectivity of this reaction. In general, the dehydration of the 5,8-epoxy Diels–Alder adducts is straightforward. Even with the basic substitution of derivatives for our interest, products may be isolated in good yield. Further work is needed to completely characterize the scope of these transformations and generalize the synthesis to less basic derivatives. The use of Lewis acid catalysts to influence the regiochemistry of the Diels–Alder reaction may also increase the generality of this approach to 6-substituted quinazolinediones.

Experimental Section

Compounds **2a–c** were prepared as previously reported.[2,3] All analytical products were homogeneous by thin-layer chromatographic analysis.

Methyl 5,8-Epoxy-5,6,7,8-tetrahydro-3-[2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl]-2,4-dioxo-1*H*,3*H*-quinazoline-*endo*-6-carboxylate (3a) and Methyl 5,8-Epoxy-5,6,7,8-tetrahydro-3-[2-[4-(2-methoxyphenyl)piperazin-1-yl]-ethyl]-2,4-dioxo-1*H*,3*H*-quinazoline-*endo*-7-carboxylate (4a). Methyl acrylate (2.67 mL, 29.7 mmol) was added to a mixture of **2a** (10.0 g, 27.0 mmol) in DMF (100 mL). The resultant mixture was stirred at room temperature for 16 h, poured into water (600 mL), and extracted with methylene chloride (2 × 100 mL). The organic solution was washed with water (3 × 200 mL) and dried over magnesium sulfate. The solvent was evaporated in vacuo, and the resultant oil was purified by flash chromatography using 3% methanol in methylene chloride as the eluant to give a mixture of **3a** and **4a**, 10.4 g (85%). The products were separated by HPLC on a 15 μm silica gel column eluted with 1.5% methanol in methylene chloride to give the product **3a**, 7.42 g (60%) as a colorless solid: mp 148–150 °C; IR 1731, 1665, and 1501 cm^{-1}; MS *m/z* 457 (MH^+); ^1H NMR ($CDCl_3$) δ 1.83 (dd, *J* = 3.90 Hz and *J* = 12.2 Hz, 1 H), 2.25 (m, 1 H), 2.60–2.90 (m, 6 H), 3.10 (m, 4 H), 3.34 (m, 1 H), 3.62 (s, 3 H), 3.85 (s, 3 H), 4.00–4.21 (m, 2 H), 5.17 (d, *J* = 5.0 Hz, 1 H), 5.57 (d, *J* = 4.6 Hz, 1 H), and 6.84–7.02 (m, 4 H). Anal. Calcd for $C_{23}H_{28}N_4O_6$: C, 60.52; H, 6.18; N, 12.27. Found: C, 60.13; H, 6.37; N, 12.03.

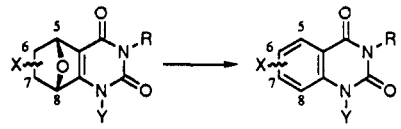
The product **4a**, 1.74 g (14%), was isolated as a colorless solid: mp 178–180 °C; IR 1721, 1647, and 1502 cm^{-1}; MS *m/z* 457 (MH^+); ^1H NMR ($CDCl_3$) δ 1.88 (dd, *J* = 3.9 Hz and *J* = 11.8 Hz, 1 H), 2.39 (m, 1 H), 2.68 (t, *J* = 7.0 Hz, 2 H), 2.78 (m, 4 H), 3.09 (m, 4 H), 3.44 (m, 1 H), 3.61 (s, 3 H), 3.86 (s, 3 H), 4.02–4.22 (m, 2 H), 5.31 (d, *J* = 5.2 Hz, 1 H), 5.47 (d, *J* = 4.4 Hz, 1 H), and 6.84–7.01 (m, 4 H). Anal. Calcd for $C_{23}H_{28}N_4O_6$: C, 60.52; H, 6.18; N, 12.27. Found: C, 60.30; H, 6.10; N, 12.02.

Methyl 5,8-Epoxy-1-methyl-5,6,7,8-tetrahydro-3-[2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl]-2,4-dioxo-1*H*,3*H*-quinazoline-*endo*-6-carboxylate (3b) and Methyl 5,8-Epoxy-1-methyl-5,6,7,8-tetrahydro-3-[2-[4-(2-methoxyphenyl)-piperazin-1-yl]ethyl]-2,4-dioxo-1*H*,3*H*-quinazoline-*endo*-7-carboxylate (4b). Furopyrimidinedione, **2c**, (2.7 g, 7.0 mmol) was treated with methyl acrylate (1.0 mL, 11.1 mmol) in DMF (40 mL) for 2 days at room temperature. The reaction was worked up as described for **3a** and **4a** to give a mixture of **3b** and **4b** as an oil, 2.5 g (77%). The products were separated by flash chromatography using 1% methanol in methylene chloride as the eluant to give the product, **3b**, which was crystallized from ether/hexane as a colorless solid, 0.91 g (28%): mp 115–117 °C; IR 1736, 1704, 1664, and 1500 cm^{-1}; MS *m/z* 471 (MH^+); ^1H NMR ($CDCl_3$) δ 1.86 (dd, *J* = 12.2 and 3.9 Hz, 1 H), 2.27–2.36 (m, 1 H), 2.53–2.82 (m, 6 H), 3.00–3.49 (m, 4 H), 3.33–3.38 (m, 1 H), 3.43 (s, 3 H), 3.62 (s, 3 H), 3.85 (s, 3 H), 4.01–4.17 (m, 2 H), 5.33 (d, *J* = 4.8 Hz, 1 H), 5.60 (d, *J* = 4.3 Hz, 1 H), and 6.83–7.01 (m, 4 H); HRMS calcd for $C_{24}H_{30}N_4O_6$ (M^+) 470.2165, found 470.2154. Anal. Calcd for $C_{24}H_{30}N_4O_6 \cdot {}^1/_2H_2O$: C, 60.11; H, 6.51; N, 11.68. Found: C, 59.92; H, 6.35; N, 11.52.

Product **4b** was isolated as an amber oil, 0.153 g (5%): IR (neat) 1730, 1706, 1664, and 1498 cm^{-1}; MS *m/z* 471 (MH^+); ^1H NMR ($CDCl_3$) δ 1.87 (dd, *J* = 11.7 and 4.1 Hz, 1 H), 2.39–2.47 (m, 1 H), 2.60–2.72 (m, 6 H), 2.97–3.16 (m, 4 H), 3.38–3.48 (m, 1 H), 3.45 (s, 3 H), 3.65 (s, 3 H), 3.86 (s, 3 H), 4.02–4.20 (m, 2 H), 5.43 (d, *J* = 4.8 Hz, 1 H), 5.49 (d, *J* = 4.5 Hz, 1 H), and 6.82–7.00 (m, 4 H); HRMS calcd for $C_{24}H_{30}N_4O_6$ (M^+) 470.2165, found 470.2149.

Conversion of 3a to 3b. Sodium hyride (60% in oil, 66 mg, 1.64 mmol) was added to a solution of **3a** (0.75 g, 1.64 mmol) in DMF (20 mL) and stirred at room temperature for 1 h. Iodomethane (0.11 mL, 1.80 mmol) was added, and the resultant solution was stirred at room temperature 1 h and poured into water (100 mL). The product was extracted into methylene chloride (2 × 50 mL), washed with water (5 × 100 mL), and dried over magnesium sulfate. The solvent was evaporated in vacuo to give an oil, which was purified by medium-pressure chromatography using 3% methanol in methylene chloride as the eluant to give the product **3b** as a colorless solid, 0.45 g (58%), identical

Table II. Dehydration of 5,8-Epoxy-5,6,7,8-tetrahydro-1*H*-quinazoline-2,4-diones to Quinazoline-2,4-diones



entry	X	Y	conditions	yield,[a] %
1	H	H	H_2SO_4/rt	63
2	6-CO_2CH_3	H	H_2SO_4/0 °C	53
3	6-CO_2CH_3	CH_3	H_2SO_4/0 °C	59
4	7-CO_2CH_3	H	H_2SO_4/rt	73
5	6-SO_2CH_3[b]	H	H_2SO_4/rt	27
6	6-CN[b,c]	H	PPA/120 °C	28
7	6,7-$(CO_2CH_3)_2$[b]	CH_3	PPA/120 °C	21
8	6,7-$(CO_2CH_3)_2$	H	PPA/120 °C	29
9	6-CN + 7-CN[b,c]	CH_3	PPA/120 °C	55[d]
10	6-SO_2CH_3 + 7-SO_2CH_3[b]	CH_3	PPA/120 °C	80[d]

[a] Yields have not been maximized. [b] Starting material was a mixture of Diels–Alder adducts described in Table I. [c] Product isolated and characterized as carboxamide. [d] Neither starting 5,8-epoxy-5,6,7,8-tetrahydro-1*H*-quinazoline-2,4-diones nor product quinazoline-2,4-diones were separable.

(12) Hydrolysis of nitriles by the action of PPA has been reported: (a) Snyder, H. R.; Elston, C. T. *J. Am. Chem. Soc.* **1954**, *76*, 3039. (b) Baldwin, S. *J. Org. Chem.* **1961**, *26*, 3280.

in all respects with the product prepared from **2c**.

Conversion of 4a to 4b. Quinazoline **4a** (0.60 g, 1.3 mmol) was treated with sodium hydride (60% in oil, 53 mg, 1.3 mmol) and iodomethane (0.09 mL, 1.4 mmol) using the procedure described for the conversion of **3a** to **3b**, to give the product **4b** as an oil, 0.53 g (86%), identical in all respects with the product prepared from **2c**.

***endo*-6-Acetyl-5,8-epoxy-5,6,7,8-tetrahydro-3-[2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl]-2,4-dioxo-1*H*,3*H*-quinazoline (Table I, Entry 3, 6-Endo) and 3-[2-[4-(2-Methoxyphenyl)piperazin-1-yl]ethyl]-7-(3-oxobut-1-yl)furo[3,4-*d*]pyrimidine-2,4-dione (6a).** Furan **2a** (8.0 g, 21.6 mmol) was treated with methyl vinyl ketone (2.0 mL, 23.9 mmol) in DMF (100 mL) for 2 days at room temperature. The reaction was worked up as described for **3a** and **4a** to give a mixture of Diels–Alder adducts (Table I, entry 3) as an oil 8.22 g (86%). The 6-endo product was isolated by flash chromatography using 2% methanol in methylene chloride as the eluant and recrystallization from acetone/water to give a colorless solid 1.6 g (17%): 166–168 °C; IR 1711, 1656, and 1501 cm^{-1}; MS *m/z* 441 (MH^+); ^1H NMR ($CDCl_3$) δ 1.96 (dd, 1 H), 2.02–2.13 (m, 1 H), 2.31 (s, 3 H), 2.63–2.84 (m, 6 H), 3.49–3.57 (m, 1 H), 3.85 (s, 3 H), 3.95–4.08 (m, 2 H), 5.13 (d, *J* = 4.9 Hz, 1 H), 5.65 (d, *J* = 4.6 Hz, 1 H), and 6.84–7.03 (m, 4 H); HRMS calcd for $C_{23}H_{28}N_4O_5$ (M^+) 440.2060, found 440.2023. Anal. Calcd for $C_{23}H_{28}N_4O_5 \cdot {}^1/_2H_2O$: C, 61.45; H, 6.50; N, 12.46. Found: C, 61.60; H, 6.50; N, 12.31. The crude fractions of the 6-endo product were combined and the solvent was evaporated in vacuo to give an oil. After 6 weeks TLC analysis indicated the product had rearranged to furan **6a**. The product was purified by flash chromatography using 2% methanol in methylene chloride as the eluant and recrystallization from acetonitrile/water to give 1.2 g (13%) of a colorless solid, mp 188–189 °C; IR 1720, 1683, 1655, and 1502 cm^{-1}; MS *m/z* 441 (MH^+); ^1H NMR ($CDCl_3$) δ 2.17 (s, 3 H), 2.68 (m, 2 H), 2.75–2.86 (m, 6 H), 2.94 (m, 2 H), 3.05–3.15 (m, 4 H), 3.85 (s, 3 H), 4.15 (m, 2 H), 6.84–7.03 (m, 4 H), 7.88 (s, 1 H), and 8.87 (br s, 1 H, exchanges with D_2O). Anal. Calcd for $C_{23}H_{28}N_4O_5$: C, 62.71; H, 6.41; N, 12.72. Found: C, 62.92; H, 6.35; N, 12.72.

***endo*-6-Acetyl-5,8-epoxy-5,6,7,8-tetrahydro-3-[2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl]-1-methyl-2,4-dioxo-1*H*,3*H*-quinazoline (Table I, Entry 4, 6-Endo).** A mixture of **2c** (3.0 g, 7.8 mmol) and with methyl vinyl ketone (1.95 mL, 23.4 mmol) in DMF (50 mL) was stirred at room temperature 4 days. The reaction was worked up as for **3a** and **4a** to give a mixture of Diels–Alder adducts (Table I, entry 4), 2.88 g (81%). The 6-endo product was isolated by medium-pressure chromatography, using 1% methanol in methylene chloride as the eluant, to give a colorless solid 1.9 g (54%): mp 146–148 °C; IR 2816, 1707, 1664, 1650, and 1500 cm^{-1}; MS *m/z* 455 (MH^+); ^1H NMR ($CDCl_3$) δ 1.98 (dd, *J* = 3.9 Hz and *J* = 12.1 Hz, 1 H), 2.08–2.17 (m, 1 H), 2.31 (s, 3 H), 2.59 (m, 2 H), 2.73 (m, 4 H), 3.07 (m, 4 H), 3.42 (s, 3 H), 3.43–3.55 (m, 1 H), 3.85 (s, 3 H), 4.01–4.11 (m, 2 H), 5.30 (d, *J* = 5.2 Hz, 1 H), 5.68 (d, *J* = 4.1 Hz, 1 H), and 6.83–7.01 (m, 4 H). Anal. Calcd for $C_{24}H_{30}N_4O_5$: C, 63.42; H, 6.65; N, 12.33. Found: C, 63.39; H, 6.74; N, 12.29.

Dimethyl 5,8-Epoxy-5,6,7,8-tetrahydro-3-[2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl]-2,4-dioxo-1*H*,3*H*-quinazoline-*endo*-6,7-dicarboxylate (Table I, Entry 9, Endo). A mixture of **2a** (2.0 g, 5.4 mmol) and dimethyl maleate (1.05 mL, 84 mmol) in DMF (40 mL) was heated to 100 °C for 1 h. The mixture was worked up as described for **3a** and **4a** to give a mixture of Diels–Alder adducts (Table I, entry 9), 2.06 g (74%). The *endo*-6,7-dicarboxylate was further purified by medium-pressure chromatography using 2% methanol in methylene chloride as the eluant, to give a colorless solid 0.73 g (26%): mp 177–179 °C; IR 1742, 1705, 1665, and 1501 cm^{-1}; MS *m/z* 515 (MH^+); ^1H NMR ($CDCl_3$) δ 2.55–2.84 (m, 6 H), 3.07 (m, 4 H), 3.52–3.57 (m, 1 H), 3.60 (s, 3 H), 3.61 (s, 3 H), 3.70–3.75 (m, 1 H), 3.85 (s, 3 H), 3.97–4.18 (m, 2 H), 5.26 (d, *J* = 4.5 Hz, 1 H), 5.56 (d, *J* = 4.6 Hz, 1 H), and 6.83–7.00 (m, 4 H); HRMS calcd for $C_{25}H_{30}N_4O_8$ (M^+) 514.2064, found 514.2064. Anal. Calcd for $C_{25}H_{30}N_4O_8 \cdot {}^1/_4H_2O$: C, 57.85; H, 5.92; N, 10.79. Found: C, 57.77; H, 6.07; N, 10.63.

5,8-Epoxy-5,6,7,8-tetrahydro-3-[2-[4-(2-methoxyphenyl)-piperazin-1-yl]ethyl]-2,4-dioxo-1*H*,3*H*-quinazoline (Table I, Entry 11). A Parr pressure reactor was charged with **2a** (2.0 g, 5.4 mmol) in DMF (40 mL) and ethylene at 100 psi and heated to 80 °C for 3 days. The reaction was cooled to room temperature, the reactor was opened, and the resultant solution was worked up as described for **3a** and **4a** to give the Diels–Alder adduct as a colorless glass, 0.86 g (40%): IR 1716, 1655, and 1501 cm^{-1}; MS *m/z* 399 (MH^+); ^1H NMR ($CDCl_3$) δ 1.45–1.52 (m, 2 H), 2.04–2.07 (m, 2 H), 2.66–2.85 (m, 6 H), 3.05–3.15 (m, 4 H), 3.86 (s, 3 H), 4.05–4.13 (m, 2 H), 5.13 (d, *J* = 4.2 Hz, 1 H), 5.44 (d, *J* = 3.6 Hz, 1 H), and 6.85–7.02 (m, 4 H). Anal. Calcd for $C_{21}H_{26}N_4O_4$: C, 63.30; H, 6.58; N, 14.06. Found: C, 62.94; H, 6.62; N, 13.85.

3-[2-[4-(2-Methoxyphenyl)piperazin-1-yl]ethyl]-1*H*,3*H*-quinazoline-2,4-dione (Table II, Entry 1). Diels–Alder adduct (Table I, entry 11) (0.50 g, 1.25 mmol) was added to concentrated sulfuric acid at room temperature and stirred for 45 min. The resultant solution was poured into ice water (100 mL) and neutralized with sodium bicarbonate. The product was extracted into 5% 2-propanol in methylene chloride (50 mL) and dried over magnesium sulfate. The solvent was evaporated in vacuo, and the residue was purified by flash chromatography using 3% methanol in methylene chloride as the eluant. The product was recrystallized from 2-propanol to give a colorless solid, 0.30 g (63%): mp 210–212 °C (lit. mp 217–218 °C); IR 1717, 1664, 1636, 1623, 1599, and 1501 cm^{-1}; MS *m/z* 381 (MH^+); ^1H NMR (DMSO-d_6) δ 2.53–2.65 (m, 6 H), 2.87–2.97 (m, 4 H), 3.77 (s, 3 H), 4.04–4.09 (m, 2 H), 6.84–6.94 (m, 4 H), 7.17–7.23 (m, 2 H), 7.63–7.68 (m, 1 H), 7.94 (dd, *J* = 1.1 Hz and *J* = 7.8 Hz, 1 H), and 11.44 (br s, 1 H, exchanges with D_2O). Anal. Calcd for $C_{21}H_{24}N_4O_3 \cdot {}^1/_2H_2O$: C, 64.76; H, 6.47; N, 14.38. Found: C, 64.78; H, 6.56; N, 14.07.

Methyl 3-[2-[4-(2-Methoxyphenyl)piperazin-1-yl]ethyl]-2,4-dioxo-1*H*,3*H*-quinazoline-6-carboxylate (Table II, Entry 2). Diels–Alder adduct **3a** (1.5 g, 3.3 mmol was dehydrated with concentrated sulfuric acid (10 mL) by using the procedure described for the preparation of Table II, entry 1. The product was recrystallized from methanol to give a colorless solid, 0.77 g (53%): mp 207–208 °C; IR 1725, 1706, 1670, and 1628 cm^{-1}; MS *m/z* 439 (MH^+); ^1H NMR (DMSO-d_6) δ 2.80–2.92 (m, 6 H), 3.06–3.17 (m, 4 H), 3.86 (s, 3 H), 3.93 (s, 3 H), 4.29 (t, *J* = 6.4 Hz, 2 H), 6.84–7.01 (m, 4 H), 7.05 (d, *J* = 8.5 Hz, 1 H), 8.20 (dd, *J* = 1.9 Hz and *J* = 8.5 Hz, 1 H), 8.70 (d, *J* = 1.9 Hz, 1 H), and 10.15 (br s, 1 H, exchanges with D_2O). Anal. Calcd for $C_{23}H_{26}N_4O_5 \cdot {}^1/_4H_2O$: C, 62.36; H, 6.03; N, 12.64. Found: C, 62.39; H, 6.08; N, 12.56.

Methyl 3-[2-[4-(2-Methoxyphenyl)piperazin-1-yl]ethyl]-1-methyl-2,4-dioxo-1*H*,3*H*-quinazoline-6-carboxylate (Table II, Entry 3). Diels–Alder adduct **3b** (0.160 g, 0.34 mmol) was treated with concentrated sulfuric acid (2 mL) as described for the preparation of Table II, entry 1, to give the product, 0.090 g (59%), after recrystallization from methylene chloride/hexane as a colorless solid: mp 159–160 °C; IR 1722, 1706, 1667, 1620, 1590, and 1502 cm^{-1}; MS *m/z* 453 (MH^+); ^1H NMR ($CDCl_3$) δ 2.72–2.83 (m, 6 H), 3.03–3.15 (m, 4 H), 3.64 (s, 3 H), 3.86 (s, 3 H), 3.95 (s, 3 H), 4.27–4.32 (m, 2 H), 6.83–7.00 (m, 4 H), 7.25 (d, *J* = 8.8 Hz, 1 H), 8.32 (dd, *J* = 8.8 Hz and *J* = 2.0 Hz, 1 H), and 8.88 (d, *J* = 2.0 Hz, 1 H). Anal. Calcd for $C_{24}H_{28}N_4O_5$: C, 63.70; H, 6.24; N, 12.38. Found: C, 63.42; H, 6.09; N, 12.20.

Methyl 3-[2-[4-(2-Methoxyphenyl)piperazin-1-yl]ethyl]-2,4-dioxo-1*H*,3*H*-quinazoline-7-carboxylate (Table II, Entry 4). Diels–Alder adduct **4a** (0.80 g, 1.75 mmol) was dehydrated with concentrated sulfuric acid (8 mL) as described for Table II, entry 1. The product was recrystallized from 2-propanol to give a colorless solid, 0.56 g (73%): mp 176–177 °C; IR 1724, 1665, 1656, 1597, and 1502 cm^{-1}; MS *m/z* 439 (MH^+); ^1H NMR (DMSO-d_6) δ 2.57–2.70 (m, 6 H), 2.90–3.00 (m, 4 H), 3.77 (s, 3 H), 3.90 (s, 3 H), 4.07 (t, *J* = 6.7 Hz, 2 H), 6.85–6.98 (m, 4 H), 7.71 (dd, *J* = 1.3 Hz and *J* = 8.2 Hz, 1 H), 7.77 (d, *J* = 1.3 Hz, 1 H), 8.06 (d, *J* = 8.2 Hz, 1 H), and 11.64 (br s, 1 H, exchanges with D_2O); HRMS calcd for $C_{23}H_{26}N_4O_5$ (M^+) 438.1903, found 438.1905. Anal. Calcd for $C_{23}H_{26}N_4O_5 \cdot {}^1/_2H_2O$: C, 61.73; H, 6.08; N, 12.52. Found: C, 61.80; H, 5.89; N, 12.52.

Dimethyl 3-[2-[4-(2-Methoxyphenyl)piperazin-1-yl]-ethyl]-2,4-dioxo-1*H*,3*H*-quinazoline-6,7-dicarboxylate (Table II, Entry 8). Diels–Alder adduct Table I, entry 9 (1.5 g, 2.9 mmol), was added to PPA (22 g) at 100 °C and stirred at this temperature for 1 h. The resultant mixture was poured into ice water (300 mL) and neutralized with sodium bicarbonate. The product was extracted into 5% isopropanol in methylene chloride

(2 × 50 mL) and dried over magnesium sulfate. The product was purified by flash chromatography using 2% methanol in methylene chloride and recrystallized from methanol to give the product as a colorless solid, 0.425 g (29%): IR 1722, 1671, 1630, and 1501 cm^{-1}; MS m/z 497 (MH^+); ^1H NMR (DMSO-d_6) δ 2.55–2.67 (m, 6 H), 2.90–2.98 (m, 4 H), 3.77 (s, 3 H), 3.84 (s, 3 H), 3.85 (s, 3 H), 4.03–4.07 (m, 2 H), 6.84–6.94 (m, 4 H), 7.31 (s, 1 H), and 8.34 (s, 1 H). Anal. Calcd for $C_{25}H_{28}N_4O_7$: C, 60.48; H, 5.68; N, 11.28. Found: C, 60.27; H, 5.95; N, 11.13.

3-[2-[4-(2-Methoxyphenyl)piperazin-1-yl]ethyl]-6-(methylsulfonyl)-1*H*,3*H*-quinazoline-2,4-dione (Table II, Entry 5). A mixture of **2a** (8.0 g, 21.5 mmol) and methyl vinyl sulfone (4.08 mL, 46.6 mmol) in DMF (100 mL) was stirred at room temperature for 4 days. The mixture was worked up as described for **3a** and **4a** to give a mixture of Diels–Alder adducts (Table I, entry 7) as a colorless glass (4.7 g, 46%); HRMS calcd for $C_{22}H_{28}N_4O_6S$ (M^+) 476.1730, found 476.1732. This mixture was used without further purification.

The mixture (1.0 g, 2.10 mmol) was dehydrated with concentrated sulfuric acid as described for Table II, entry 1, to give the product as a colorless solid after recrystallization from 2-propanol, 0.263 g (27%): mp 216–220 °C; IR 1732, 1647, 1622, and 1501 cm^{-1}; MS m/z 459 (MH^+); ^1H NMR (DMSO-d_6) δ 2.55–2.63 (m, 6 H), 2.91–2.99 (m, 4 H), 3.25 (s, 3 H), 3.76 (m, 3 H), 4.04–4.09 (m, 2 H), 6.85–6.94 (m, 4 H), 7.36 (d, J = 8.6 Hz, 1 H), 8.14 (dd, J = 2.1 Hz and J = 8.6 Hz, 1 H), 8.39 (d, J = 2.1 Hz, 1 H), and 11.91 (br s, 1 H, exchanges with D_2O). Anal. Calcd for $C_{22}H_{26}N_4O_5S$: C, 57.63; H, 5.72; N, 12.22. Found: C, 57.34; H, 5.65; N, 11.99.

6-Carbamoyl-3-[2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl]-1*H*,3*H*-quinazoline-2,4-dione (Table II, Entry 6). A mixture of **2a** (8.0 g, 21.6 mmol) and acrylonitrile (3.1 mL, 23.8 mmol) in DMF (100 mL) was stirred at room temperature for 5 days. The resultant solution was worked up as described for **3a** and **4a** to give a mixture of Diels–Alder adducts (Table I, entry 5), 7.42 g (81%); HRMS calcd for $C_{22}H_{25}N_5O_4$ (M^+) 423.1907, found 423.1904. This mixture was used without further purification.

The mixture (1.0 g, 2.36 mmol) was dehydrated with PPA as described for Table II, entry 8, to give the product as a colorless solid after recrystallization from methanol/DMSO (0.27 g, 28%): mp 268–271 °C; IR 1726, 1719, 1680, 1671, 1655, 1602, and 1500 cm^{-1}; MS m/z 424 (MH^+); ^1H NMR (DMSO-d_6) δ 2.53–2.70 (m, 6 H), 2.88–3.01 (m, 4 H), 3.77 (s, 3 H), 4.05–4.14 (m, 2 H), 6.85–6.95 (m, 4 H), 7.20 (d, J = 8.5 Hz, 1 H), 7.40 (br s, 1 H, exchanges with D_2O), 8.13 (m, 2 H, simplifies to dd, J = 1.9 Hz and J = 8.5 Hz, 1 H with D_2O), 8.51 (d, J = 1.9 Hz, 1 H), 11.67 (br s, 1 H, exchanges with D_2O). Anal. Calcd for $C_{22}H_{25}N_5O_4$: C, 62.40; H, 5.95; N, 16.54. Found: C, 62.13; H, 5.78; N, 16.27.

Dimethyl 3-[2-[4-(2-Methoxyphenyl)piperazin-1-yl]ethyl]-1-methyl-2,4-dioxo-1*H*,3*H*-quinazoline-6,7-dicarboxylate (Table II, Entry 7). A mixture of **2c** (2.0 g, 5.20 mmol) and dimethyl maleate (0.85 mL, 6.76 mmol) in DMF (40 mL) was heated to 80 °C for 8 h. The reaction was worked up as described for **3a** and **4a** to give a mixture of Diels–Alder adducts (Table I, entry 10), 1.90 g (68%); HRMS calcd for $C_{26}H_{32}N_4O_8$ (M^+) 528.2220, found 528.2255. The mixture was used without further purification.

The mixture (1.0 g, 1.89 mmol) was dehydrated with PPA (20 g) as described for Table II, entry 8, to give the product, after trituration in diethyl ether, as a colorless solid, 0.205 g (21%): mp 161–163 °C; IR 1729, 1716, 1665, 1623, and 1500 cm^{-1}; MS m/z 511 (MH^+); ^1H NMR ($CDCl_3$) δ 2.73–2.85 (m, 6 H), 3.05–3.15 (m, 4 H), 3.64 (s, 3 H), 3.86 (s, 3 H), 3.93 (s, 3 H), 3.97 (s, 3 H), 4.27–4.31 (m, 2 H), 6.83–6.99 (m, 4 H), 7.35 (s, 1 H), and 8.73 (s, 1 H). Anal. Calcd for $C_{26}H_{30}N_4O_7$: C, 61.17; H, 5.92; N, 10.97. Found: 61.22; H, 6.02; N, 10.90.

6-Carbamoyl-3-[2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl]-1-methyl-1*H*,3*H*-quinazoline-2,4-dione and 7-Carbamoyl-3-[2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl]-1-methyl-1*H*,3*H*-quinazoline-2,4-dione (Table II, Entry 9). A mixture of furan **2c** (3.0 g, 7.8 mmol) and acrylonitrile (1.6 mL, 18.6 mmol) was heated in DMF (40 mL) to 80 °C for 4 h. The resultant solution was worked up as described for **3a** and **4a** to give a mixture of Diels–Alder adducts (Table I, entry 6), 3.33 g (98%), as a colorless glass; HRMS calcd for $C_{23}H_{27}N_5O_4$ (M^+) 437.2063, found 437.2040. The mixture was used without further purification.

The mixture (1.0 g, 2.28 mmol) was dehydrated with PPA (30 g) as described for Table II, entry 8, to give a mixture of the 6-carboxamido and the 7-carboxamido products as a colorless solid, 0.64 g (80%): IR 1709, 1654, 1616, 1584, 1514, and 1499 cm^{-1}; MS m/z 438 (MH^+); ^1H NMR (6-carboxamido) (DMSO-d_6) δ 2.55–2.67 (m, 6 H), 2.90–2.98 (m, 4 H), 3.55 (s, 3 H), 3.78 (s, 3 H), 4.10–4.18 (m, 2 H), 6.85–6.98 (m, 4 H), 7.46 (br s, 1 H), 7.52 (d, J = 8.8 Hz, 1 H), 8.21 (br s, 1 H), 8.24 (dd, J = 2.1 Hz and J = 8.8 Hz, 1 H), and 8.60 (d, J = 2.1 Hz, 1 H); (7-carboxamido) δ 2.55–2.67 (m, 6 H), 2.90–2.98 (m, 4 H), 3.58 (s, 3 H), 3.78 (s, 3 H), 4.10–4.18 (m, 2 H), 6.85–6.98 (m, 4 H), 7.71 (br s, 1 H), 7.74 (dd, J = 1.0 Hz and J = 8.1 Hz, 1 H), 7.84 (d, J = 1.0 Hz, 1 H), 8.10 (d, J = 8.1 Hz, 1 H) and 8.21 (br s, 1 H). Anal. Calcd for $C_{23}H_{27}N_5O_4$: C, 63.14; H, 6.22; N, 16.00. Found: C, 62.98; H, 5.98; N, 15.76.

3-[2-[4-(2-Methoxyphenyl)piperazin-1-yl]ethyl]-1-methyl-6-(methylsulfonyl)-1*H*,3*H*-quinazoline-2,4-dione and 3-[2-[4-(2-Methoxyphenyl)piperazin-1-yl]ethyl]-1-methyl-7-(methylsulfonyl)-1*H*,3*H*-quinazoline-2,4-dione (Table II, Entry 10). A mixture of furan **2c** (2.0 g, 5.20 mmol) and methyl vinyl sulfone (2 mL, 22.8 mmol) in DMF (40 mL) was stirred at room temperature for 3 days. The resultant solution was worked up as described for **3a** and **4a** to give a mixture of Diels–Alder adducts (Table I, entry 8), 1.88 g (74%), as a colorless glass; HRMS calcd for $C_{23}H_{30}N_4O_6S$ (M^+) 490.1886, found 490.1884. The mixture was used without further purification.

The mixture (0.83 g, 1.69 mmol) was dehydrated with PPA (20 g) as described for Table II, entry 8, to give a mixture of the 6-(methylsulfonyl) and the 7-(methylsulfonyl) products as a colorless solid, 0.64 g (80%): IR 1709, 1663, 1610, and 1500 cm^{-1}; MS m/z 473 (MH^+); ^1H NMR (6-methylsulfonyl) (DMSO-d_6) δ 2.55–2.65 (m, 6 H), 2.90–2.97 (m, 4 H), 3.29 (s, 3 H), 3.61 (s, 3 H), 3.76 (s, 3 H), 4.10–4.15 (m, 2 H), 6.85–6.97 (m, 4 H), 7.70 (d, J = 8.9 Hz, 1 H), 8.24 (dd, J = 2.3 Hz and J = 8.9 Hz, 1 H), and 8.49 (d, J = 2.3 Hz, 1 H); (7-methylsulfonyl) δ 2.55–2.65 (m, 6 H), 2.90–2.97 (m, 4 H), 3.36 (s, 3 H), 3.57 (s, 3 H), 3.76 (s, 3 H), 4.10–4.15 (m, 2 H), 6.85–6.97 (m, 4 H), 7.80 (dd, J = 1.4 Hz and J = 8.2 Hz, 1 H), 7.88 (d, J = 1.4 Hz, 1 H), and 8.28 (d, J = 8.2 Hz, 1 H); HRMS calcd for $C_{23}H_{28}N_4O_5S$ (M^+) 472.1780, found 472.1782.

Methyl 3-[2-[4-(2-Methoxyphenyl)piperazin-1-yl]ethyl]-furo[3,4-*d*]pyrimidine-2,4-dione-1-*trans*-propenoate (5). A mixture of **2a** (4.0 g, 10.8 mmol) and methyl propiolate (1.1 mL, 12 mmol) in DMF (50 mL) was stirred at room temperature 16 h. The resultant solution was worked up as described for **3a** and **4a** to give the product as a colorless solid, 4.8 g (97%), after recrystallization from acetonitrile/water: mp 168–170 °C; IR 1736, 1690, 1643, 1623, 1544, and 1498 cm^{-1}; MS m/z 455 (MH^+); ^1H NMR ($CDCl_3$) δ 2.71–2.83 (m, 6 H), 3.05–3.13 (m, 4 H), 3.82 (s, 3 H), 3.86 (s, 3 H), 4.23 (t, J = 6.7 Hz, 2 H), 5.94 (d, J = 14.7 Hz, 1 H), 6.85–7.04 (m, 4 H), 7,81 (d, J = 1.5 Hz, 1 H), 8.21 (d, J = 1.5 Hz, 1 H), and (d, J = 14.7 Hz, 1 H). Anal. Calcd for $C_{23}H_{26}N_4O_6 \cdot {}^1/_4H_2O$: C, 60.18; H, 5.81; N, 12.21. Found: C, 60.09; H, 5.66; N, 12.13.

3-[2-[4-(2-Methoxyphenyl)piperazin-1-yl]ethyl]-1-methyl-7-(3-oxobut-1-yl)furo[3,4-*d*]pyrimidine-2,4-dione (6b). Diels–Alder adduct Table I, entry 4, 6-endo (1.0 g, 2.20 mmol), was added to concentrated sulfuric acid (8 mL) at room temperature and stirred for 30 min. The resultant solution was poured into ice water (100 mL) and neutralized with sodium bicarbonate. The product was extracted into 5% 2-propanol in methylene chloride and dried over magnesium sulfate. The solvent was evaporated in vacuo, and the residue was purified by flash chromatography using 3% methanol in methylene chloride to give the product as a colorless solid, 0.43 g (43%): mp 119–120 °C; IR 1718, 1668, 1653, 1566, and 1500 cm^{-1}; MS m/z 455 (MH^+); ^1H NMR ($CDCl_3$) δ 2.18 (s, 3 H), 2.67–2.84 (m, 6 H), 2.89 (t, J = 7.0 Hz, 2 H), 3.04–3.16 (m, 4 H), 3.18 (t, J = 7.02 Hz, 2 H), 3.59 (s, 3 H), 3.85 (s, 3 H), 4.13–4.19 (m, 2 H), 6.83–7.01 (m, 4 H), and 7.93 (s, 1 H). Anal. Calcd for $C_{24}H_{30}H_4O_5$: C, 63.42; H, 6.65; N, 12.32. Found: C, 63.44; H, 6.77; N, 12.30.

Conversion of Table I, Entry 3, 6-Endo, to 6a in Sulfuric Acid. Diels–Alder adduct Table I, entry 3, 6-endo (1.2 g, 2.67 mmol), was treated with concentrated sulfuric acid (15 mL) as

described for Table II, entry 1, to give the product **6a**, 0.55 g (47%), as a colorless solid, identical in all respects with the product prepared from **2a**.

1-[2-(Methoxycarbonyl)ethyl]-3-[2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl]thieno[3,4-*d*]pyrimidine-2,4-dione (7).[3] Thienopyrimidine **2b** (0.77 g, 2 mmol) was treated with methyl acrylate (0.2 mL, 2 mmol) in DMF (15 mL) at room temperature for 24 h. The resultant solution was worked up as described for **3a** and **4a** to give the product, 0.93 g (99%), as a colorless solid: mp 140-141 °C;[3] IR (KBr) 2820, 1700, 1655, 1580, and 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.6-3.2 (m, 12 H), 3.67 (s, 3 H), 3.83 (s, 3 H), 4.03-4.33 (m, 4 H), 6.73 (d, J = 3 Hz, 1 H), 6.83-7.0 (m, 4 H), and 8.25 (d, J = 3 Hz, 1 H). Anal. Calcd for $C_{23}H_{28}N_4O_5S$: C, 58.45; H, 5.97; N, 11.86. Found: C, 58.21; H, 6.08; N, 11.89.

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Evidence for Intramolecular Electrostatic Catalysis as a Possible Mechanism in the Hydrolysis of Vinyl Ethers in Aqueous Solution

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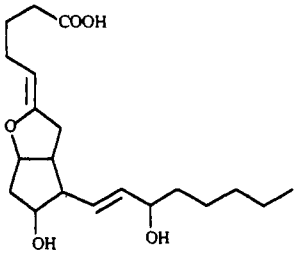
The hydrolysis of the vinyl ether functional group in 2-methoxybicyclo[2.2.2]oct-2-ene-1-carboxylic acid (**2**) has been found to be catalyzed by intramolecular electrostatic catalysis by the carboxylate ion of the substrate.[1] The rate constant ratios of the charged and the neutral form of the substrate are 32.3 and 31.2 for catalysis by hydronium ion and acetic acid, respectively. This is in contrast to ratios that have been found for vinyl ethers hydrolyzed by intramolecular general-acid catalysis, where large rate ratios for catalysis by hydronium ion but small rate ratios, normally a factor 2, when catalyzed by acetic acid are observed. The solvent isotope effect, 3.4 ± 0.5, is close to what has been predicted for electrostatic catalysis in the hydrolysis of prostacyclin (**1**).

Electrostatic catalysis has been discussed as a possible mechanism in enzymatic reactions and also in the hydrolysis of the vinyl ether function of prostacyclin (**1**). However, electrostatic interactions are small in aqueous solution, and it is therefore difficult to unambigiously detect electrostatic catalysis with small molecules in that medium. All evidence presented in the kinetic investigations of prostacyclin[2] and different model compounds for prostacyclin[3-5] are in favor of intramolecular general-acid catalysis as the mechanism in the hydrolysis of the vinyl ether function.

By synthesizing a vinyl ether compound in which electrostatic stabilization of the developing oxocarbonium ion is achieved, and where, at the same time, intramolecular general-acid catalysis is excluded, it has been possible to demonstrate that electrostatic catalysis is a possible mechanism in the hydrolysis of vinyl ethers even in aqueous solution. Thus, with the compound 2-methoxybicyclo[2.2.2]oct-2-ene-1-carboxylic acid (**2**), we still obtained a considerable rate increase upon ionization of the carboxylic acid group. The only possible explanation for this behavior is that the vinyl ether function is hydrolyzed through intramolecular electrostatic catalysis during intermolecular protonation.

Experimental Section

^1H NMR spectra were recorded on a Varian XL 400 instrument with a modified transmitter and computer system. Chemical shifts are given in ppm downfield from Me_4Si. Semipreparative HPLC was performed with a Waters Associates System consisting of a Waters M-45 solvent delivery system, a Waters U6K injector, a



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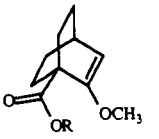
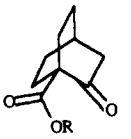


2 R=H, Na
3 R=CH_3



4 R=CH_3
5 R=H

R-sil silica column (10 μm particles, 4.6 mm (i.d.) × 25 cm) and a Waters R-401 differential refractometer.

Synthetic Procedure. The bicyclic vinyl ether **3** was synthesized from the known ketone **4**[6] by O-alkylation of the enolate formed from **4** using potassium hydride as the base. Ketone **4** was synthesized from crotonaldehyde and dimethylamine in 11 steps using the procedures described in refs 6-8. Ketone **4** is also the product formed in the hydrolysis of the vinyl ether **3**.

Methyl 2-oxobicyclo[2.2.2]octane-1-carboxylate (4): mp (from hexane) 63.6-64.1 °C (lit.[6] mp 62.5-64.5 °C); NMR (C_6D_6) ^1H δ 1.05-1.22 (m, 4 H), 1.42-1.48 (quint, 1 H, J = 3 Hz, >C*H*CH_2C=O), 1.51-1.64 (m, 2 H), 1.84-1.87 (dd, 2 H, J = 3 and

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