Antiallergy Agents. 1. Substituted 1,8-Naphthyridin-2(1*H*)-ones as Inhibitors of SRS-A Release

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A novel class of antiallergy agents, the substituted 1,8-naphthyridin-2(1*H*)-ones, is described. The present compounds are orally active, potent inhibitors of allergic and nonallergic bronchospasm in animal models. Structure–activity studies of the lead compound in this series, 1-phenyl-3-*n*-butyl-4-hydroxynaphthyridin-2(1*H*)-one (**11**), identified three compounds of interest, 1-phenyl-3-(2-propenyl)-4-acetoxy-1,8-naphthyridin-2(1*H*)-one (**12**), 1-(3′-chlorophenyl)-3-(2-propenyl)-4-acetoxy-1,8-naphthyridin-2(1*H*)-one (**87**), and 1-(3′-methoxyphenyl)-3-(2-propenyl)-4-acetoxy-1,8-naphthyridin-2(1*H*)-one (**89**). The mechanism of antiallergy activity may involve inhibition of the release of the sulfidopeptide leukotrienes. 1-Phenyl-3-(2-propenyl)-4-acetoxy-1,8-naphthyridin-2(1*H*)-one, Sch 33303 (**12**), was selected for preclinical development as an antiallergy agent.

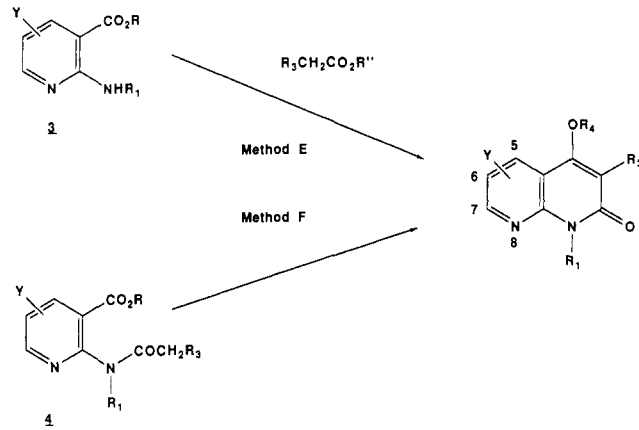
Human asthma is characterized clinically as recurrent wheezing dyspnea occurring in patients with bronchial hyperreactivity to a variety of stimuli. There is reversible airway obstruction due in part to a spasm of airway smooth muscle and to inflammatory edema. Extrinsic asthma in humans, which can be simulated in animal models, is precipitated by exposure of sensitized individuals to a specific antigen with the resultant IgE-induced release of certain bronchospastic and inflammatory mediators. In contrast, intrinsic asthma, which comprises a significant percentage of the asthmatic population, is caused by nonallergic stimuli, such as cold or exercise.

Among the diverse autacoids that have been implicated as mediating the bronchospasm in allergic bronchial asthma are histamine, serotonin, bradykinin, prostaglandins and slow-reacting substance of anaphylaxis (SRS-A). Following the development of clinically useful antihistamines, it was found that these agents had little effect on allergic bronchospasm in humans, thereby questioning the importance of histamine as a bronchospastic mediator in human asthma.[1] With the further knowledge that human airway smooth muscle is relatively insensitive to serotonin, and human asthma is not generally ameliorated by antiserotonins, antihistamines or inhibitors of prostaglandin synthesis, recent interest has turned to other mediators, such as SRS-A and platelet activating factor (PAF), or to the need to suppress a combination of these spasmogens.

Since the early observations of Kellaway and Trethwie[2] that immunological challenge of sensitized guinea pig lung caused the release of SRS-A, this mediator has been implicated in the pathophysiology of bronchial asthma.[3-5] The importance of SRS-A has been confirmed in more recent studies, which show the release of SRS-A from asthmatic lung[6] and the potent bronchoconstrictor effects of SRS-A on human airway smooth muscle in vitro[7,8] and in vivo.[9-11]

The oxygenation and subsequent metabolism of arachidonic acid in a variety of cell types occurs via two major metabolic pathways, the cyclooxygenase that yields prostaglandins and thromboxanes, and the 5-lipoxygenase that converts arachidonic acid into LTB_4, a chemotactic diol, and the sulfidopeptide leukotrienes (LT) LTC_4, LTD_4, and LTE_4. The transient autacoids, LTC_4 and LTD_4, are the major bronchospastic components of SRS-A.[12-15] Despite their limited biological half-life, the sulfidopeptide leukotrienes produce prolonged bronchospasm caused by slow dissociation from their receptors.[16,17] Therefore, it is possible that the identification and development of compounds that inhibit the formation of the sulfidopeptide

Scheme I. Synthesis of Substituted 1,8-Naphthyridin-2(1*H*)-ones



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‡ Department of Chemistry, Duke University, Durham, NC 27706.

(1) Herzig, D. J. In *New Drug Discovery and Development*; Rubin, A. A., Ed.; Marcel Dekker: New York, 1978; p 29.
(2) Kellaway, C. H.; Trethwie, E. R. *Quat. J. Exp. Physiol.* **1940**, *30*, 121.
(3) Orange, R. P.; Austen, K. F. In *Advances in Immunology*; Dixon, F. J., Kunkel, H. G., Ed.; Academic: New York, 1969, Vol. 10, p 105–144.
(4) Goetzl, E. J. *N. Engl. J. Med.* **1980**, *303*, 822.
(5) Kreutner, W.; Siegel, M. I. In *Annual Reports in Medicinal Chemistry*; Bailey, D. M., Ed.; Academic: New York, 1984; Vol. 19, pp 241–252.
(6) Dahlen, S. E.; Hansson, G.; Hedquist, P.; Bjorck, T.; Granstron, E.; Dahlen, B. *Proc. Natl. Acad. Sci. U.S.A.* **1983**, *80*, 1712.
(7) Dahlen, S. E.; Bjorck, J.; Hedquist, P.; Arfors, K. E.; Hammarstram, S.; Lindgreen, J. A. and Samuelsson, B., *Proc. Natl. Acad. Sci.* **1981**, 78, 3887.
(8) Hedquist P.; Dahlen, S. E.; Gustafsson, L.; Hammarstrom, S.; Samuelsson, B. *Acta Physiol. Scand.* **1980**, *110*, 331.
(9) Holroyde, M. C.; Altouynyan, R. E. C.; Cole, M.; Dixon, M.; Elliott, E. V. *Lancet.* **1981**, *2*, 17.
(10) Weiss, J. W.; Drazen, J. M.; Cole, N. *Science (Washington, D.C.)* **1982**, *216*, 196.
(11) Griffin, M.; Weiss, J. W.; Leitch, A. G.; McFadden, E. R.; Corey, E. J.; Austen, K. F.; Drazen, J. M. *N. Engl. J. Med.* **1983**, *308*, 436.
(12) Murphy, R. C.; Hammarstron, S.; Samuelson, B. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 4275.
(13) Hammarstron, S.; Samuelsson, B.; Clark, D. A.; Goto, G.; Marafat, A.; Miokowski, C.; Corey, E. J. *Biochem. Biophys. Res. Commun* **1980**, *92*, 946.
(14) Morris, H. R.; Taylor, G. W.; Piper, P. J.; Samhoun, M. N.; Tippins, J. R. *Prostaglandins* **1980**, *19*, 185.

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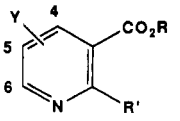
Table I. Substituted Nicotinic Acids and Derivatives (1)



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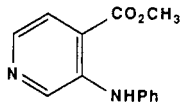
compd	R′	R	Y	formula	ref
1a	Cl	H	H	$C_6H_4ClNO_2$	*a*
1b	Cl	CH_3	H	$C_7H_6ClNO_2$	18
1c	Cl	CH_3CH_2	H	$C_8H_8ClNO_2$	19
1d	NH_2	H	H	$C_6H_6N_2O_2$	*a*
1e	NH_2	CH_3CH_2	H	$C_8H_{10}N_2O_2$	20
1f	Cl	H	6-CH_3	$C_7H_6ClNO_2$	21
1g	Cl	H	5-Br	$C_6H_3BrClNO_2$	22
1h	Cl	H	5,6-$(CH_2)_3$	$C_9H_8ClNO_2$	23
1i	Cl	H	5,6-$(CH_2)_4$	$C_{10}H_{10}ClNO_2$	23

[a] Available from the Aldrich Chemical Co.

leukotrienes will lead to new therapeutic approaches for prophylactic treatment of bronchial asthma and other conditions, such as allergic rhinitis where these mediators are elaborated.

As part of our directed efforts to discover novel antiinflammatory agents, a series of substituted 1,8-naphthyridin-2(1*H*)-ones was identified by screening that represents a unique class of antiallergy agents. The compounds reported are orally active, potent inhibitors of allergic and nonallergic bronchospasm in animal models. The former activity has been attributed to inhibition of the elaboration of sulfidopeptide leukotrienes. Development of this series led to the selection of 1-phenyl-3-(2-propenyl)-4-acetoxy-1,8-naphthyridin-2(1*H*)-one, Sch 33303 (**12**), for preclinical development as a potential antiallergy drug.



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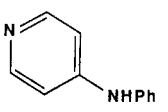

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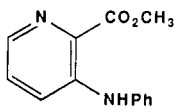

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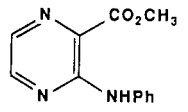

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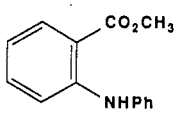

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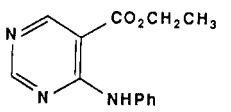
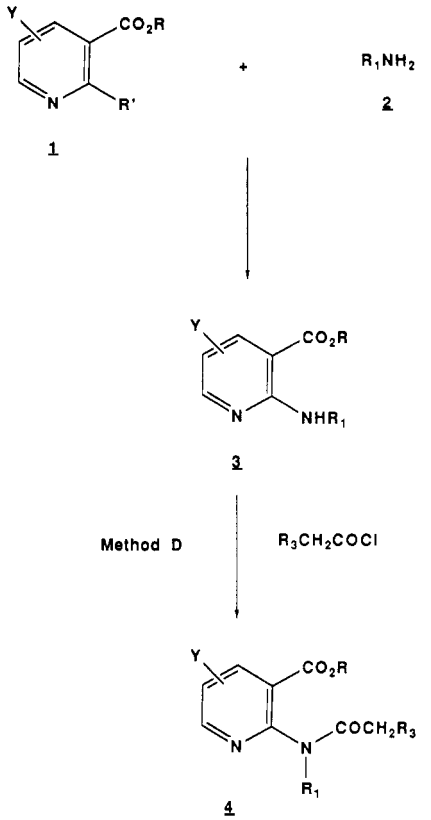


10

Chemistry

The substituted 1,8-naphthyridin-2(1*H*)-ones and congeners described in Table IV were generally prepared by two procedures (Scheme I). Treatment of a substituted pyridine (**3**) or congener (Table II) with the appropriate ester in the presence of potassium *tert*-butoxide gave the corresponding substituted 1,8-naphthyridin-2(1*H*)-ones directly (**11**, **13**, **14**, **17**, **19**, **21–25**, **27–29**, **34–38**, **42–45**, **47**, **48**, **52**, **56**, **57**, **63**, **64**, **68**, **73**, **74**, **95**, **97–101**, **105**, and **109**, method E). Alternatively, the substituted pyridine (**3**) or congener was treated with the appropriate acylating agent to produce the corresponding *N*-acylpyridine (**4**) (Table III, method D, Scheme II). Subsequent treatment of the *N*-acylpyridine (**4**) with potassium *tert*-butoxide gave the corresponding substituted 1,8-naphthyridin-2(1*H*)-ones,

Scheme II. Synthesis of Substituted Pyridines



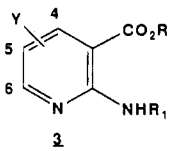
11, **39**, **41**, **60**, **67**, **70–72**, **75**, **93**, **94**, and **96** (method F, Scheme I).

The required nicotinic acids and esters described in Table I, and the substituted amines described in the experimental section were either commercially available or their method of preparation has been described previously.[18-23] The substituted pyridines (**3**) and congeners described in Table II were prepared by the procedures described by Kermack and Weatherhead[24] or Nantka-Namirsky,[25] respectively.

Following the general methods C, G–J and the specific experimental procedures described (see the Experimental

(15) Morris, H. R.; Taylor, G. W.; Piper, P. J.; Tippins, J. R. *Nature (London)* **1980**, *285*, 104.
(16) Pong, S. S.; DeHaven, R. N. *Proc. Natl. Acad. Sci. U.S.A.* **1983**, *80*, 7415.
(17) Pong, S. S.; DeHaven, R. N.; Kuehl, F. A., Jr.; Egan, R. W. *J. Biol. Chem.* **1983**, *258*, 9616.
(18) Bowden, K. J.; Grank, G.; Ross, W. J. *J. Chem. Soc. C.* **1969**, 172.
(19) Sliwa, H.; Maitte, P., *C. R. Hebol. Seances Acad. Sci.* **1964**, *259*, 2255.
(20) Fox, H. H. *J. Org. Chem.* **1952**, *17*, 547.
(21) Nantka-Namirsky, P.; Piechaczak, J. Pol. **1970**, *60*, 438; *Chem. Abstr.* **1974**, *74*, 64214*h*.
(22) Setliff, F. *J. Chem. Eng. Data* **1970**, *15*, 590.
(23) Godar, E. M.; Mariella, R. P. *J. Org. Chem.* **1960**, *25*, 557.
(24) Kermack, W. O.; Weatherhead, A. P. *J. Chem. Soc.* **1942**, 726.
(25) Nantka-Namirsky, P. *Acta. Pol. Pharm.* **1967**, *24*, 111.
(26) Bachman, G. B.; Barker, R. S. *J. Org. Chem.* **1949**, *14*, 97.
(27) Jerchel, D.; Jakob, L. *Chem. Ber.* **1958**, *91*, 1266.
(28) Dunn, G. E.; Thimm, H. F. *Can. J. Chem.* **1977**, *55*, 1342.
(29) Bohme, H. *Arch. Pharm.* **1960**, *293*, 1011.
(30) Sherlock, M. U.S. Pat. 4492702, 1985; *Chem. Abstr.* **1985**, *102*, 132018*w*.
(31) Juby, P. F.; Hudyma, T. W. *J. Med. Chem.* **1967**, *10*, 954.
(32) Ziegler, E.; Maier, H. *Montash. Chem.* **1958**, *89*, 551.
(33) Blythin, D. J.; Kaminski, J. J.; Domalski, M. S.; Spitler, J.; Solomon, D. M.; Conn, D. J.; Wong, S. C.; Verbiar, L. L.; Bober, L. A.; Chiu, P. J. S.; Watnick, A. S.; Siegel, M. I.; Hilbert, J. M.; McPhail, A. T. *J. Med. Chem.* **1986**, *29*, 1099.
(34) Kim, D. H. *J. Heterocycl. Chem.* **1974**, *11*, 703.
(35) Doering, W. E.; Weil, R. A. N. *J. Am. Chem. Soc.* **1947**, *69*, 2461.

Table II. Substituted Pyridines (3) and Congeners

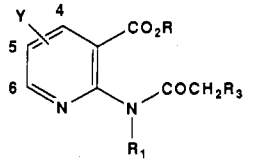


3

compd	R_1	R	Y	method of synthesis	mp, °C	recrystn solvent	yield, %	formula	anal.
3a	2-$CH_3OC_6H_4$	H	H	A	185–187	CH_3CN	92	$C_{13}H_{12}N_2O_3$	C, H, N
3b	3-$CH_3OC_6H_4$	H	H	A	161–163	CH_3CN	92	$C_{13}H_{12}N_2O_3$	C, H, N
3c	4-$CH_3OC_6H_4$	H	H	A	207–208	CH_3CN	86	$C_{13}H_{12}N_2O_3$	C, H, N
3d	3,4,5-$(CH_3O)_3C_6H_2$	H	H	A	154–156	CH_3CN	79	$C_{15}H_{16}N_2O_5$	C, H, N
3e	4-$nC_4H_9OC_6H_4$	H	H	A	175–177	CH_3CN	90	$C_{16}H_{18}N_2O_3$	C, H, N
3f	4-$PhOC_6H_4$	H	H	A	194–196	CH_3CN	86	$C_{18}H_{14}N_2O_3$	C, H, N
3g	4-$PhCH_2OC_6H_4$	H	H	A	188–190	CH_3CN	84	$C_{19}H_{16}N_2O_3$	C, H, N
3h	2-$CH_3SC_6H_4$	H	H	A	134–135	iPr_2O	79	$C_{13}H_{12}N_2O_2S$	C, H, N
3i	3-$CH_3SC_6H_4$	H	H	A	173–174	$(CH_3)_2CO$	96	$C_{13}H_{12}N_2O_2S$	C, H, N
3j	4-$CH_3SC_6H_4$	H	H	A	198–200	$(CH_3)_2CO$	70	$C_{13}H_{12}N_2O_2S$	C, H, N
3k	2-$CH_3C_6H_4$	H	H	A	165–167	*a*	72	$C_{13}H_{12}N_2O_2$	
3l	2,6-$(CH_3)_2C_6H_3$	H	H	A	209–211	CH_3OH–Et_2O	23	$C_{14}H_{14}N_2O_2$	C, H, N
3m	4-*n*-$C_4H_9C_6H_4$	H	H	A	175–176	CH_3CN	95	$C_{16}H_{18}N_2O_2$	C, H, N
3n	3,4$(CH_2)_3C_6H_3$	H	H	A	169–170	$(CH_3)_2CO$	80	$C_{15}H_{14}N_2O_2$	C, H, N
3o	4-FC_6H_4	H	H	A	193–194	CH_3CN	93	$C_{12}H_9FN_2O_2$	C, H, N
3p	2,4-$F_2C_6H_3$	H	H	A	185–186	CH_3CN	93	$C_{12}H_8F_2N_2O_2$	C, H, N
3q	3-ClC_6H_4	H	H	A	199–201	iPrOAc	75	$C_{12}H_9ClN_2O_2$	C, H, N
3r	4-$CH_3COC_6H_4$	H	H	A	213–214	CH_3OH	94	$C_{14}H_{12}N_2O_3$	C, H, N
3s	3-CO_2H,4-OHC_6H_3	H	H	A	275–278 dec	DMF–H_2O	81	$C_{13}H_{10}N_2O_5$	C, H, N
3t	3-Py	H	H	A	275–277	HOAc	49	$C_{11}H_9N_3O_2$	C, H, N
3u	$PhCH_2$	H	H	A	238–240	EtOH	91	$C_{13}H_{12}N_2O_2$	C, H, N
3v	*n*-C_6H_{13}	H	H	A	143–145	CH_3CN–CH_3OH	28	$C_{12}H_{18}N_2O_2$	C, H, N
3w	$(CH_3)_2N(CH_2)_2$	H	H	A	*b*		60	$C_{10}H_{15}N_3O_2$	
3x	C_6H_5	H	6-CH_3	A	156–158	CH_3CN	83	$C_{13}H_{12}N_2O_2$	C, H, N
3y	C_6H_5	H	5-Br	A	205–206	CH_3CN	76	$C_{12}H_9BrN_2O_2$	C, H, N
3z	C_6H_5	H	5,6-$(CH_2)_3$	A	229–231	CH_3CN	93	$C_{15}H_{14}N_2O_2$	C, H, N
3aa	C_6H_5	H	5,6-$(CH_2)_4$	A	238–239	CH_3CN	85	$C_{16}H_{16}N_2O_2$	C, H, N
3bb	C_6H_5	CH_3	H	B	*c*		92	$C_{13}H_{12}N_2O_2$	C, H, N
3cc	C_6H_5	CH_3CH_2	H	B	52–54	EtOH	73	$C_{14}H_{14}N_2O_2$	C, H, N
3dd	3,4-$(CH_3O)_2C_6H_3$	CH_3CH_2	H	B	78–79	EtOH	51	$C_{16}H_{18}N_2O_4$	C, H, N
3ee	3-$CF_3C_6H_4$	CH_3	H	B	72–74	CH_3OH	98	$C_{14}H_{11}F_3N_2O_2$	C, H, N
3ff	2-CH_3,3-ClC_6H_3	CH_3CH_2	H	B	90–92	EtOH	76	$C_{15}H_{15}ClN_2O_2$	C, H, N
3gg	2-$CH_3OC_6H_4$	CH_3	H	C	118–120	CH_3OH	91	$C_{14}H_{14}N_2O_3$	C, H, N
3hh	3-$CH_3OC_6H_4$	CH_3	H	C	54–55	CH_3OH	85	$C_{14}H_{14}N_2O_3$	C, H, N
3ii	4-$CH_3OC_6H_4$	CH_3	H	C	80–83	CH_3OH	93	$C_{14}H_{14}N_2O_3$	C, H, N
3jj	3,4,5-$(CH_3O)_3C_6H_2$	CH_3	H	C	117–118	CH_3OH	92	$C_{16}H_{18}N_2O_5$	C, H, N
3kk	4-*n*-$C_4H_9OC_6H_4$	CH_3	H	C	63–65	CH_3OH	92	$C_{17}H_{20}N_2O_3$	C, H, N
3ll	4-$PhOC_6H_4$	CH_3	H	C	86–88	CH_3OH	91	$C_{19}H_{16}N_2O_3$	C, H, N
3mm	3-$PhCH_2OC_6H_4$	CH_3	H	C	118–119	CH_3OH	97	$C_{20}H_{18}N_2O_3$	C, H, N
3nn	2-$CH_3SC_6H_4$	CH_3	H	C	73–74	iPr_2O	90	$C_{14}H_{14}N_2O_2S$	C, H, N
3oo	3-$CH_3SC_6H_4$	CH_3	H	C	60–61	hexane	96	$C_{14}H_{14}N_2O_2S$	C, H, N
3pp	4-$CH_3SC_6H_4$	CH_3	H	C	84–85	iPr_2O	95	$C_{14}H_{14}N_2O_2S$	C, H, N
3qq	2-$CH_3C_6H_4$	CH_3	H	C	94–96	Et_2O–hexane	80	$C_{14}H_{14}N_2O_2$	
3rr	2,6-$(CH_3)_2C_6H_3$	CH_3	H	C	132–134	Et_2O–hexane	51	$C_{15}H_{16}N_2O_2$	
3ss	4-*n*-$C_4H_9C_6H_4$	CH_3	H	C	*d*		98	$C_{17}H_{20}N_2O_2$	C, H, N
3tt	3,4-$(CH_2)_3C_6H_3$	CH_3	H	C	94–95	*i*-Pr_2O	98	$C_{16}H_{16}N_2O_2$	C, H, N
3uu	4-FC_6H_4	CH_3	H	C	78–80	CH_3OH	89	$C_{13}H_{11}FN_2O_2$	C, H, N
3vv	2,4-$F_2C_6H_3$	CH_3	H	C	98–100	CH_3OH	97	$C_{13}H_{10}F_2N_2O_2$	C, H, N
3ww	3-ClC_6H_4	CH_3CH_2	H	C	49–51	CH_3OH	84	$C_{14}H_{13}ClN_2O_2$	C, H, N
3xx	4-$CH_3COC_6H_4$	CH_3	H	C	98–100	iPr_2O	90	$C_{15}H_{14}N_2O_3$	C, H, N
3yy	3-CO_2CH_3,4-OHC_6H_3	CH_3	H	C	113–114	iPr_2O	87	$C_{15}H_{14}N_2O_5$	C, H, N
3zz	3-Py	CH_3	H	C	92–93	iPr_2O	99	$C_{12}H_{11}N_3O_2$	C, H, N
3aaa	$PhCH_2$	CH_3	H	C	*e*		88	$C_{14}H_{14}N_2O_2$	C, H, N
3bbb	*n*-C_6H_{13}	CH_3	H	C	88–89	CH_2Cl_2–Et_2O	99	$C_{13}H_{20}N_{20}$·2HCl	C, H, N
3ccc	$(CH_3)_2N(CH_2)_2$	CH_3CH_2	H	B	*f*		76	$C_{12}H_{19}N_3O_2$	C, H, N
3ddd	C_6H_5	CH_3	6-CH_3	C	53–54	H_2O	95	$C_{14}H_{14}N_2O_2$	C, H, N
3eee	C_6H_5	CH_3	5-Br	C	96–97	CH_3OH	85	$C_{13}H_{11}BrN_2O_2$	C, H, N
3fff	C_6H_5	CH_3	5,6-$(CH_2)_3$	C	119–121	$(CH_3)_2CO$	98	$C_{16}H_{16}N_2O_2$	C, H, N
3ggg	C_6H_5	CH_3	5,6-$(CH_2)_4$	C	95–96	CH_3OH	95	$C_{17}H_{18}N_2O_2$	C, H, N
3hhh	C_6H_5	CH_3	5-OH	Ex[g]	154–156	Et_2O–hexane	14	$C_{13}H_{12}N_2O_3$	C, H, N
3iii	C_6H_5	CH_3	5,6-C_4H_4	Ex	100–101	hexane	80	$C_{17}H_{14}N_2O_2$	C, H, N
5				C[26]	*h*		99	$C_{13}H_{12}N_2O_2$	C, H, N
6				ref 27				$C_{11}H_{10}N_2$	
7				C[28]	96–97	iPr_2O	57	$C_{13}H_{12}N_2O_2$	C, H, N
8				ref 29				$C_{14}H_{13}NO_2$	
9				ref 30				$C_{12}H_{11}N_3O_2$	
10				ref 31				$C_{13}H_{13}N_3O_2$	

[a] Isolated and used without further purification unless otherwise indicated. [b] Isolated as an oil. [c] Bp 158–162 °C (0.5 mmHg). [d] Bp 196–197 °C (1.2 mmHg). [e] Bp 137–141 °C (0.08 mmHg). [f] Bp 145–150 °C (3 mmHg). [g] Ex = experimental procedure described. [h] Bp 168–170 °C (0.15 mmHg).

Table III. N-Acylated Pyridines (4)



4

compd	R_1	R_3	R	Y	mp, °C	recrystn[a] solvent	yield, %	formula	anal.
4a	C_6H_5	H	CH_3	H	119–120	iPrOAc	85	$C_{15}H_{14}N_2O_3$	C, H, N
4b	C_6H_5	CH_3	CH_3	H	94–95	hexane	80	$C_{16}H_{16}N_2O_3$	C, H, N
4c	C_6H_5	$CH_3(CH_2)_3$	CH_3	H	82–83	hexane	69	$C_{19}H_{22}N_2O_3$	C, H, N
4d	C_6H_5	$CH_3(CH_2)_4$	CH_3	H	52–53	hexane	66	$C_{20}H_{24}N_2O_3$	C, H, N
4e	$2\text{-}CH_3OC_6H_4$	H	CH_3	H	109–110	hexane	82	$C_{16}H_{16}N_2O_4$	C, H, N
4f	$3\text{-}CH_3OC_6H_4$	H	CH_3	H	88–89	iPr_2O	97	$C_{16}H_{16}N_2O_4$	C, H, N
4g	$4\text{-}CH_3OC_6H_4$	H	CH_3	H	78–80	iPrOAc	87	$C_{16}H_{16}N_2O_4$	C, H, N
4h	$4\text{-}CH_3OC_6H_4$	$CH_3(CH_2)_3$	CH_3CH_2	H	*b*		60	$C_{21}H_{26}N_2O_4$	C, H, N
4i	$3,4\text{-}(CH_3O)_2C_6H_3$	$CH_3(CH_2)_3$	CH_3CH_2	H	72–74	iPrOAc	61	$C_{22}H_{28}N_2O_5$	C, H, N
4j	$4\text{-}FC_6H_4$	$CH_3(CH_2)_3$	CH_3	H	91–92	hexane	53	$C_{19}H_{21}FN_2O_3$	C, H, N
4k	$2,4\text{-}F_2C_6H_3$	$CH_3(CH_2)_3$	CH_3	H	95–96	hexane	39	$C_{19}H_{20}F_2N_2O_3$	C, H, N
4l	$3\text{-}CF_3C_6H_4$	H	CH_3	H	*c*		99	$C_{16}H_{13}F_3N_2O_3$	C, H, N
4m	$2\text{-}CH_3,3\text{-}ClC_6H_3$	$CH_3(CH_2)_3$	CH_3CH_2	H	*c*		89	$C_{21}H_{25}ClN_2O_3$	

[a] Isolated and used without further purification unless otherwise indicated. [b] Bp 210–211 °C (0.45 mmHg). [c] Isolated as an oil.

Section), the remaining substituted 1,8-naphthyridin-2-(1*H*)-ones and congeners described in Table IV were prepared.

The competition between C- versus O-alkylation of a β-dicarbonyl system has been an extensively studied reaction in organic synthesis. In order to establish unequivocally the site of alkylation in the substituted 1,8-naphthyridin-2(1*H*)-one system, 1-phenyl-3-*n*-butyl-4-(2-hydroxyethoxy)-1,8-naphthyridin-2(1*H*)-one (**115**), obtained from reaction of 1-phenyl-3-*n*-butyl-4-hydroxynaphthyridin-2(1*H*)-one (**11**) with bromoethanol, was subjected to single-crystal X-ray analysis. The crystal structure was solved by direct methods.[36] Full-matrix least-squares refinement of atomic parameters[37] converged at $R = 0.035$ ($R_w = 0.052$)[38] over 2544 reflections. A view of the structure and solid-state conformation of **115** is provided in Figure 1. The results indicate that alkylation of the β-dicarbonyl system in **11** occurred exclusively at oxygen atom O_{20}. This observation is in contrast to the regiospecific C-alkylation, which occurred in the β-dicarbonyl system of a remotely related heterocyclic class.[39] Bond lengths and angles in **115** all lie close to expected values. The 1,8-naphthyridine ring atoms (N_1–C_{8a}) have a root mean square deviation of only 0.018 Å from their least-squares plane and thus are approximately coplanar. Directly bonded C_9 and C_{16} ($\Delta = 0.68$ Å) deviate slightly from it. The dihedral angle between the N_1–C_{8a} least-squares plane and that through the phenyl ring atoms (C_9–C_{14}) is 80.0°. Whereas the *n*-butyl side chain is in a fully extended form, the O_{20}–C_{21}–C_{22}–O_{23} torsion angle is −56.5°, and thus the hydroxyethyl moiety has a conformation in accord with that expected on the basis of a strong "gauche effect".[40]

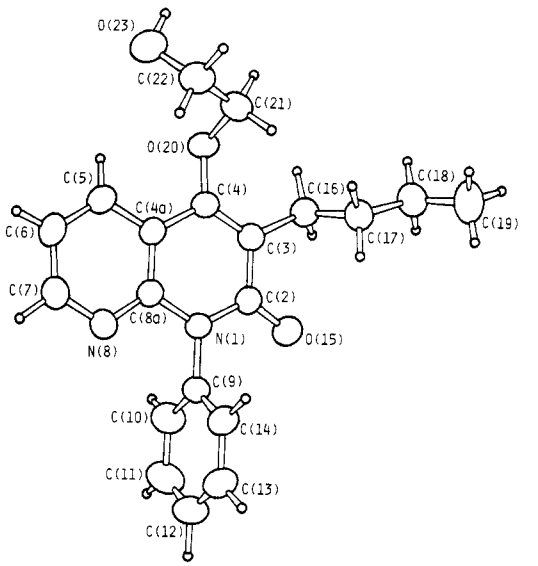


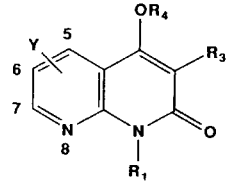
Figure 1. Structure and solid-state conformation of 1-phenyl-3-*n*-butyl-4-(2-hydroxyethoxy)-1,8-naphthyridin-2(1*H*)-one (**115**); small circles represent hydrogen atoms.

Biological Test Methods

The compounds were evaluated for their antiallergy activity in two models (Table IV). The release of SRS-A in vitro from guinea pig lung was used as the primary screen to assess antiallergy activity. In this test, the compounds were examined at a concentration of 10 μM, and the amount of SRS-A released was measured by bioassay. Those compounds that inhibited the release of SRS-A by greater or equal to 50% were examined in the secondary screen, the SRS-A mediated anaphylactic bronchospasm in guinea pigs. The SRS-A component of the anaphylactic bronchospasm was enhanced by treating sensitized guinea pigs prior to antigen challenge with mepyramine to block the effects of released histamine, with indomethacin to block the formation of dilator and constrictor prostaglandins and thromboxane and with pro-

(36) Crystallographic calculations were performed on PDP11/44 and Microvax II computers by use of the Enraf-Nonius Structure Determination Package incorporating MULTAN11/82.
(37) Supplementary material, see the paragraph at the end of the paper.
(38) $R = \sum||F_o| - |F_c||/\sum|F_o|$; $R_w = [\sum w(|F_o|)^2/\sum w|F_o|^2]^{1/2}$.
(39) Solomon, D. M.; Conn, D. J.; Wong, S. C.; Kaminski, J. J. *Heterocycles* **1986**, *24*, 2179.
(40) Wolfe, S. *Acc. Chem. Res.* **1972**, *5*, 102.

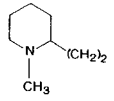
Table IV. Substituted 1,8-Naphthyridin-2(1*H*)-ones and Congeners



no.	R_1	R_3	R_4	Y	synth meth	mp, °C	recrystn solvent	yield, %	formula[a]	in vitro % inhibn of SRS-A release, 10 μM	in vivo % inhibn of bronchospasm: oral dose, mg/kg 25	12.5
11	C_6H_5	n-C_4H_9	Na	H	E or F	245–262		95	$C_{18}H_{17}N_2O_2$-Na-$^3/_4H_2O$	56[b]		68[c]
12	C_6H_5	$CH_2CH{=}CH_2$	CH_3CO	H	H	195–196	EtOH	52	$C_{19}H_{16}N_2O_3$	73[d]		84[e]
13	C_6H_5	n-C_4H_9	H	5,6,7,8-tetrahydro	E	190–192	HOAc–H_2O	45	$C_{18}H_{22}N_2O_2$	51	17	
14					E	234–236	MeOH	84	$C_{18}H_{18}N_2O_2$	0		
15					Ex	198–200	MeCN	16	$C_{18}H_{18}N_2O_2$	0		
16					Ex	234–236	MeCN	14	$C_{18}H_{18}N_2O_2$	31		
17					E	119–120	iPr_2O	25	$C_{18}H_{18}N_2O_2$	43		
18									$C_{19}H_{19}NO_2$			
19					E	183–185	EtOAc–hexane	64	$C_{17}H_{17}N_3O_2$	75	36	
20					Ex	172–173	iPr_2O	57	$C_{18}H_{17}N_3O_2$	69	10	
21					E	202–203	EtOAc	52	$C_{17}H_{17}N_3O_2$	9		
22	C_6H_5	n-C_4H_9	H	7-CH_3	E	281–283	EtOH	55	$C_{19}H_{20}N_2O_2$	21		
23	C_6H_5	n-C_4H_9	H	6,7-$(CH_2)_3$	E	239–240	MeOH	74	$C_{21}H_{22}N_2O_2$	22		
24	C_6H_5	n-C_4H_9	H	6,7-$(CH_2)_4$	E	233–234	MeCN	49	$C_{22}H_{24}N_2O_2$	38		
25	C_6H_5	n-C_4H_9	H	6,7-(C_4H_4)	E	278–279	EtOH	82	$C_{22}H_{20}N_2O_2$	0		
26	C_6H_5	n-C_4H_9	H	6-CH_3O	Ex	181–182	EtOAc–hexane	80	$C_{19}H_{20}N_2O_3$	3		
27	C_6H_5	n-C_4H_9	H	6-OH	E	299–300	EtOAc–hexane	52	$C_{18}H_{18}N_2O_3$	69	0	
28	C_6H_5	n-C_4H_9	H	6-Br	E	188–190	MeCN	81	$C_{18}H_{17}BrN_2O_2$	73	5	
29	C_6H_5	H	H	6-Br	E	314–317	EtOH	73	$C_{14}H_9BrN_2O_2$			
30	C_6H_5	H	H	6-CH_3O	Ex	285–287	MeOH	62	$C_{15}H_{12}N_2O_3$			
31	C_6H_5	H	$CH_2CH{=}CH_2$	6-CH_3O	G	157–158	EtOH	25	$C_{18}H_{16}N_2O_3$			
32	C_6H_5	$CH_2CH{=}CH_2$	CH_3CO	6-CH_3O	H	164–166	EtOH	89	$C_{20}H_{18}N_2O_4$	0		
33	C_6H_5	$CH_2CH{=}CH_2$	H	6-OH	Ex	241–243	MeCN	71	$C_{17}H_{14}N_2O_3$	55	18	
34	H	n-C_4H_9	H	H	E	222–223	EtOH	76	$C_{12}H_{14}N_2O_2$	15		
35	n-C_6H_{13}	n-C_4H_9	H	H	E	125–126	EtOAc	41	$C_{18}H_{26}N_2O_2$	63	15	
36	$PhCH_2$	n-C_4H_9	H	H	E	147–149	MeCN	53	$C_{19}H_{20}N_2O_2$	0		
37	3-Py	n-C_4H_9	H	H	E	218–219	MeCN	15	$C_{17}H_{17}N_3O_2$	33		
38	$(CH_3)_2N(CH_2)_2$	n-C_4H_9	H	H	E	81–84	MeCN	60	$C_{16}H_{23}N_3O_2$·$^1/_2H_2O$	0		
39	4-$CH_3OC_6H_4$	n-C_4H_9	H	H	F	257–259	MeCN	76	$C_{19}H_{20}N_2O_3$	87	51	
40	4-$CH_3OC_6H_4$	n-C_4H_9	CH_3CO	H	J	184–185	EtOAc	89	$C_{21}H_{22}N_2O_4$	64	32	
41	3,4-$(CH_3O)_2C_6H_3$	n-C_4H_9	H	H	F	214–215	MeOH	45	$C_{20}H_{22}N_2O_4$	57	0	
42	3,4,5-$(CH_3O)_3C_6H_2$	n-C_4H_9	H	H	E	185–186	MeCN	66	$C_{21}H_{24}N_2O_5$	22		
43	4-n-$C_4H_9OC_6H_4$	n-C_4H_9	H	H	E	242–243	EtOH	69	$C_{22}H_{26}N_2O_3$	17		
44	4-$PhOC_6H_4$	n-C_4H_9	H	H	E	243–244	EtOH	41	$C_{24}H_{22}N_2O_3$	54	0	
45	4-$PhCH_2OC_6H_4$	n-C_4H_9	H	H	E	261–262	EtOH	79	$C_{25}H_{24}N_2O_3$	50	0	
46	4-HOC_6H_4	n-C_4H_9	H	H	Ex	290–292	MeCN	57	$C_{18}H_{18}N_2O_3$	44		
47	2-$CH_3SC_6H_4$	n-C_4H_9	H	H	E	201–202	MeCN	10	$C_{19}H_{20}N_2O_2S$	32		
48	3-$CH_3SC_6H_4$	n-C_4H_9	H	H	E	245–246	pyridine	89	$C_{19}H_{20}N_2O_2S$	62	55	
49	3-$CH_3SC_6H_4$	n-C_4H_9	CH_3CO	H	J	142–143	acetone–	99	$C_{21}H_{22}N_2O_3S$	57	27	

50	3-$CH_3SOC_6H_4$	n-C_4H_9	CH_3CO	H	Ex	166–168	EtOAc–hexane	72	$C_{21}H_{22}N_2O_4S$	28		
51	3-$CH_3SO_2C_6H_4$	n-C_4H_9	CH_3CO	H	Ex	201–202	EtOAc	93	$C_{21}H_{22}N_2O_5S$	20		
52	4-$CH_3SC_6H_4$	n-C_4H_9	H	H	E	262–263	MeOH	79	$C_{19}H_{20}N_2O_2S$	86	8	
53	4-$CH_3SC_6H_4$	n-C_4H_9	CH_3CO	H	J	208–210	MeCN	98	$C_{21}H_{22}N_2O_3S$	38		
54	4-$CH_3SOC_6H_4$	n-C_4H_9	CH_3CO	H	Ex	218–219	EtOH	50	$C_{21}H_{22}N_2O_4S$	11		
55	4-$CH_3SO_2C_6H_4$	n-C_4H_9	CH_3CO	H	Ex	185–186	EtOAc	20	$C_{21}H_{22}N_2O_5S$	26		
56	2-$CH_3C_6H_4$	n-C_4H_9	H	H	E	195–197	EtOAc	52	$C_{19}H_{20}N_2O_2$	55	9	
57	4-$C_4H_9{}^nC_6H_4$	n-C_4H_9	H	H	E	237–239	EtOH	71	$C_{22}H_{26}N_2O_2$	50	13	
58	4-$CH_3COC_6H_4$	n-C_4H_9	H	H	Ex	267–269	EtOAc	46	$C_{20}H_{20}N_2O_3$	37		
59	4-$CH_3CH(OH)C_6H_4$	n-C_4H_9	H	H	Ex	258–259	MeOH	62	$C_{20}H_{22}N_2O_3$	48		
60	4-FC_6H_4	n-C_4H_9	H	H	F	282–283	MeOH	94	$C_{18}H_{17}FN_2O_2$	85		0
61	4-FC_6H_4	n-C_4H_9	CH_3CO	H	J	184–185	hexane	47	$C_{20}H_{19}FN_2O_3$	77		34
62	2,4-FC_6H_3	n-C_4H_9	H	H	F	207–208	MeCN	8	$C_{18}H_{16}F_2N_2O_2$	27		
63	3,4-$(CH_2)_3C_6H_3$	n-C_4H_9	H	H	E	250–251	EtOH	66	$C_{21}H_{22}N_2O_2$	55	1	
64	3-CO_2Et,4-OHC_6H_3	n-C_4H_9	H	H	E	194–195	EtOH–iPr_2O	9	$C_{21}H_{22}N_2O_5$	65		0
65	3-CO_2H,4-OHC_6H_3	n-C_4H_9	H	H	Ex	274–276	EtOH–iPr_2O	70	$C_{19}H_{18}N_2O_5$	0		
66	3-CO_2H,4-$AcOC_6H_3$	n-C_4H_9	CH_3CO	H	J	165–167	acetone–hexane	92	$C_{23}H_{22}N_2O_7$	17		
67	2-CH_3,3-ClC_6H_3	n-C_4H_9	H	H	F	227–228	MeCN	50	$C_{19}H_{19}ClN_2O_2$	5		
68	2,6-$(CH_3)_2C_6H_3$	n-C_4H_9	H	H	E	250–252	MeOH	63	$C_{20}H_{22}N_2O_2$	0		
69					Ex	127–130	Et_2O–hexane	72	$C_{18}H_{16}N_2O_2$	14		
70	2-$CH_3OC_6H_4$	H	H	H	F	281–282	EtOH	57	$C_{15}H_{12}N_2O_3 \cdot {}^1/_4H_2O$			
71	3-$CH_3OC_6H_4$	H	H	H	F	261–262	EtOH	74	$C_{15}H_{12}N_2O_3$			
72	4-$CH_3OC_6H_4$	H	H	H	F	307–310	MeOH	80	$C_{15}H_{12}N_2O_3$			
73	4-$PhCH_2OC_6H_4$	H	H	H	E	274–276	MeOH	42	$C_{21}H_{16}N_2O_3$			
74	3-ClC_6H_4	H	H	H	E	>270	EtOH	73	$C_{14}H_9ClN_2O_2$			
75	3-$CF_3C_6H_4$	H	H	H	F	295–297	EtOH	72	$C_{15}H_9F_3N_2O_2$			
76	C_6H_5	H	$CH_2CH{=}CH_2$	H	G	176–177	MeOH	47	$C_{17}H_{14}N_2O_2$			
77	2-$CH_3OC_6H_4$	H	$CH_2CH{=}CH_2$	H	G	163–164	EtOH	17	$C_{18}H_{16}N_2O_3$			
78	3-$CH_3OC_6H_4$	H	$CH_2CH{=}CH_2$	H	G	158–159	EtOH	20	$C_{18}H_{16}N_2O_3$			
79	4-$CH_3OC_6H_4$	H	$CH_2CH{=}CH_2$	H	G	201–202	EtOH	50	$C_{18}H_{16}N_2O_3$			
80	4-$PhCH_2OC_6H_4$	H	$CH_2CH{=}CH_2$	H	G	188–189	MeCN	76	$C_{24}H_{20}N_2O_3$			
81	3-ClC_6H_4	H	$CH_2CH{=}CH_2$	H	G	134–136	iPrOAc	48	$C_{17}H_{13}ClN_2O_2$			
82	3-$CF_3C_6H_4$	H	$CH_2CH{=}CH_2$	H	G	162–164	EtOH	52	$C_{18}H_{13}F_3N_2O_2$			
83	2-$CH_3OC_6H_4$	$CH_2CH{=}CH_2$	CH_3CO	H	H	135–136	iPr_2O	63	$C_{20}H_{18}N_2O_4$	35		
84	3-$CH_3OC_6H_4$	$CH_2CH{=}CH_2$	CH_3CO	H	H	148–149	EtOH	83	$C_{20}H_{18}N_2O_4$	84		32
85	4-$CH_3OC_6H_4$	$CH_2CH{=}CH_2$	CH_3CO	H	H	183–184	EtOH	86	$C_{20}H_{18}N_2O_4$	52	42	
86	4-$PhCH_2OC_6H_4$	$CH_2CH{=}CH_2$	CH_3CO	H	H	181–183	EtOAc	84	$C_{26}H_{22}N_2O_4$	*f*		
87	3-ClC_6H_4	$CH_2CH{=}CH_2$	CH_3CO	H	H	108–110	EtOH	54	$C_{19}H_{15}ClN_2O_3$	60[g]	*h*	
88	3-$CF_3C_6H_4$	$CH_2CH{=}CH_2$	CH_3CO	H	H	105–107	iPr_2O–hexane	90	$C_{20}H_{15}F_3N_2O_3$	65		
89	3-$CH_3OC_6H_4$	$CH_2CH{=}CH_2$	H	H	I	206–207	EtOH	93	$C_{18}H_{16}N_2O_3$	69[i]	90[j]	
90	3-$CH_3OC_6H_4$	$CH_2CH{=}CH_2$	H	H	I	228–229	$CHCl_3$	95	$C_{18}H_{16}N_2O_3$	56	46	
91	4-$CH_3OC_6H_4$	$CH_2CH{=}CH_2$	H	H	I	253–255	EtOH	35	$C_{18}H_{16}N_2O_3$	3		
92	3-$CF_3C_6H_4$	$CH_2CH{=}CH_2$	H	H	H	198–200	MeCN	81	$C_{18}H_{13}F_3N_2O_2$	50	0	
93	C_6H_5	H	H	H	F	309–310	MeOH	93	$C_{14}H_{10}N_2O_2$	0		
94	C_6H_5	CH_3	H	H	F	>320	EtOH	20	$C_{15}H_{12}N_2O_2$	52	33	
95	C_6H_5	CH_3CH_2	H	H	E	314–3159 dec	MeCN	87	$C_{16}H_{14}N_2O_2$	74		44
96	C_6H_5	n-C_5H_{11}	H	H	F	226–228	MeCN	67	$C_{19}H_{20}N_2O_2$	49	42	
97	C_6H_5	n-C_8H_{17}	H	H	E	181–182	MeOH–iPr_2O	75	$C_{22}H_{26}N_2O_2$	51	0	
98	C_6H_5	C_6H_{11}	H	H	E	292–294	EtOAc	29	$C_{20}H_{20}N_2O_2$	66	45	
99	C_6H_5	$CH_2C_6H_{11}$	H	H	E	289–291	EtOH	76	$C_{21}H_{22}N_2O_2$	30		
100	C_6H_5	C_6H_5	H	H	E	248–249	MeCN	77	$C_{20}H_{14}N_2O_2$	48		
101	C_6H_5	$C_6H_5(CH_2)_4$	H	H	E	198–199	EtOH	62	$C_{24}H_{22}N_2O_2$	9		
102	C_6H_5	$CH_3C(O_2C_2H_4)(CH_2)_2$	H	H	Ex	180–182	EtOAc	45	$C_{20}H_{20}N_2O_4$	52	0	
103	C_6H_5	$CH_3CO(CH_2)_2$	H	H	Ex	182–184	MeOH–Et_2O	86	$C_{18}H_{16}N_2O_3$	36		

Table IV (Continued)

no.	R_1	R_3	R_4	Y	synth meth	mp, °C	recrystn solvent	yield, %	formula[a]	in vitro % inhibn of SRS-A release, 10 μM	in vivo % inhibn of bronchospasm: oral dose, mg/kg	
											25	12.5
104	C_6H_5	$CH_3CH(OH)(CH_2)_2$	H	H	Ex	234–235	EtOAc–MeOH	53	$C_{18}H_{18}N_2O_3$	53	32	
105	C_6H_5	2-Py	H	H	E	332–333	pyridine	76	$C_{19}H_{13}N_3O_2$	84		42
106	C_6H_5	2-Py$(CH_2)_2$	H	H	Ex	255–257 dec	EtOH	86	$C_{21}H_{17}N_3O_2$	58		5
107	C_6H_5		CH_3CO	H	Ex	196–197	MeCN	35	$C_{24}H_{27}N_3O_3 \cdot H_2O$	19		
108	C_6H_5	$CH_2CH{=}CH_2$	H	H	I	251–252	$CHCl_3$	93	$C_{17}H_{14}N_2O_2$	81	85[k]	
109	C_6H_5	$(CH_2)_7CH{=}CH_2$	CH_3CO	H	E,I	139–141	EtOAc	69	$C_{25}H_{28}N_2O_3$	15		
110	C_6H_5	$CH_2CH{=}C(CH_3)_2$	H	H	E	250–260		95	$C_{19}H_{17}N_2O_2Na \cdot H_2O$	45		
111	C_6H_5	n-C_4H_9	CH_3CH_2	H	G	171–172	MeCN	60	$C_{20}H_{22}N_2O_2$	0		
112	C_6H_5	n-C_4H_9	$CH_3CH_2O(CH_2)_2$	H	G	110–113	EtOAc–hexane	50	$C_{22}H_{26}N_2O_3$	0		
113	C_6H_5	n-C_4H_9	$(CH_3)_2CO_2(CH_2CH)CH_2$	H	G	127–129	iPr_2O	43	$C_{24}H_{28}N_2O_4$	0		
114	C_6H_5	n-C_4H_9	$HOCH_2CH(OH)CH_2$	H	Ex	161–163	MeCN	86	$C_{21}H_{24}N_2O_4$	0		
115	C_6H_5	n-C_4H_9	$HOCH_2CH_2$	H	G	136–138	iPr_2O	40	$C_{20}H_{22}N_2O_3$	86	64	
116	C_6H_5	n-C_4H_9	$HO(CH_2)_3$	H	G	173–175	acetone	87	$C_{21}H_{24}N_2O_3$	7		
117	C_6H_5	n-C_4H_9	$(CH_3)_2N(CH_2)_2 \cdot HCl$	H	G	236–238	EtOH	47	$C_{22}H_{28}ClN_3O_2$	0	84	13
118	C_6H_5	n-C_4H_9	$(CH_3)_2N(CH_2)_3 \cdot HCl$	H	G	197–199	MeCN	33	$C_{23}H_{30}ClN_3O_2$	0	13	
119	C_6H_5	n-C_4H_9	$CH_2CH{=}CH_2$	H	G	138–140	iPr_2O	26	$C_{21}H_{22}N_2O_2$	0		
120	C_6H_5	n-C_4H_9	$CH_2C{\equiv}CH$	H	G	102–104	EtOAc–hexane	24	$C_{21}H_{20}N_2O_2$	0		
121	C_6H_5	$CH_2C{\equiv}CH$	$CH_2C{\equiv}CH$	H	G	173–175	EtOAc	6	$C_{20}H_{14}N_2O_2$	62		0
Doxantrazole			DSCG[l]								38	0
Proxicromil[m]											17	
Aminophylline										*n*		
FPL55712[43]											*o*	

[a] All compounds gave satisfactory elemental analysis (carbon, hydrogen, nitrogen, and sodium ±0.4%) for the empirical formula indicated. [b] IC_{50} (μM) = 0.24(0.01–19), $p = 0.05$. [c] Oral ED_{50} (mg/kg) = 14; although the regression is significant the correlation is low. [d] IC_{50} (μM) = 1.1(0.7 – 2.0), $p = 0.05$. [e] Oral ED_{50} (mg/kg) = 2.9(1.3 – 7.6), $p = 0.05$. [f] Percent inhibition = 23 at 3 μM. [g] IC_{50} (μM) = 1, approximate. [h] Oral ED_{50} (mg/kg) = 0.4, approximate. [i] IC_{50} (μM) = 0.98(0.05 – 14), $p = 0.05$. [j] Oral ED_{50} (mg/kg) = 3.7(0.9 – 12.8), $p = 0.05$. [k] Cyanosis observed during pharmacologic evaluation of test drug. [l] Percent inhibition of bronchospasm by DSCG administered intravenously at 10 mg/kg was 0. [m] Percent inhibition of bronchospasm by Proxicromil administered intravenously at 5 mg/kg was 0. [n] Percent inhibition of bronchospasm by Aminophylline administered orally at 160, 53, and 18 mg/kg was 81, 55, and 21, respectively. [o] Percent inhibition of bronchospasm by FPL55712 administered intravenously at 5, 2.5, and 1 mg/kg was 68, 57, and 32, respectively.

pranolol to potentiate the resultant bronchospasm due to formed SRS-A.[41] In this test, compounds were administered orally to sensitized guinea pigs 12.5–25 mg/kg, 2 h prior to antigen challenge. The effect of the test compound on anaphylactic bronchospasm is expressed as percent inhibition of the peak increase in intratracheal pressure compared to the peak increase in the control group.

Results and Discussions

1-Phenyl-3-*n*-butyl-4-hydroxy-1,8-napthyridin-2(1*H*)-one (**11**) was identified initially as a compound of interest on the basis of its acute antiinflammatory activity in the reverse passive Arthus reaction (RPAR) in the rat paw.[42] The potency of **11** in the RPAR assay was 0.6 (0.3–0.9) times indomethacin at a confidence level of 95%; the relative potency of indomethacin equals 1.0. This significant level of antiinflammatory activity led to an evaluation of the antiallergy activity of **11** as well.

Compound **11** was a potent inhibitor of antigen stimulated SRS-A release from actively sensitized guinea pig lung, IC_{50} = 0.24 (0.01–19) μM (Table IV). In contrast, disodiumchromoglycate (DSCG) and similar inhibitors of mediator release, such as doxantrazole and proxicromil, produce little or no inhibition at comparable concentrations.

In a model of leukotriene-mediated anaphylactic bronchospasm in guinea pigs, **11** provided significant protection from the allergic pulmonary response, approximate oral ED_{50} = 14 mg/kg (Table IV). DCSG and proxicromil were inactive when given intravenously, and doxantrazole was inactive when given orally. Significant inhibition of the allergic bronchospasm in this model is provided by aminophylline and the putative SRS-A receptor antagonist, FPL 55712.[43] At oral doses of 25–50 mg/kg, **11** did not inhibit the bronchospasm to injected LTC_4, indicating its activity against an anaphylactic bronchospam was probably due to inhibition of the generation of bronchospastic leukotrienes rather than bronchodilation or end-organ antagonism of leukotriene action.

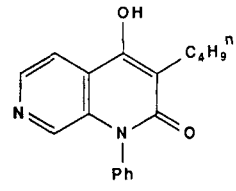
The interesting antiallergy activity of the prototype of this series, compound **11**, led to a structure–activity study to identify a more potent orally active analogue. The in vitro and in vivo antiallergy activities determined for the substituted 1,8-naphthyridin-2(1*H*)-ones and congeners are described in Table IV. In general, there appears to be good correlation between the antiallergy activity observed in the in vitro and in vivo models. In only one instance was an in vitro inactive analogue (1-phenyl-3-*n*-butyl-4-(2-(*N*,*N*-dimethylamino)ethoxy)-1,8-naphthyridin-2(1*H*)-one, **117**) active when tested in vivo.

However, in this case, **117** may be metabolically transformed to **11**, which could be the active species in vivo.[44-47] The following compounds were the most potent substituted 1,8-naphthyridin-2(1*H*)-ones identified: 1-phenyl-3-(2-propenyl)-4-acetoxy-1,8-naphthyridin-2(1*H*)-one (**12**), 1-(3′-chlorophenyl)-3-(2-propenyl)-4-acetoxy-1,8-naphthridin-2(1*H*)-one (**87**), and 1-(3′-methoxyphenyl)-3-(2-propenyl)-4-acetoxy-1,8-naphthyridin-2(1*H*)-one (**89**).

Structure–Activity Relationships

The in vitro antiallergy activity described in Table IV suggests the following structure–activity relationships.

Skeletal Framework. The necessity of the 1,8-naphthyridin-2(1*H*)-one ring system to maintain antiallergy activity in the series was investigated with the preparation of the tetrahydro analogue **13**, the nitrogen atom positional isomers **14**, **15**, and **17**, respectively, and the carbocyclic analogue **18**. In addition, isosteric replacement of an aromatic carbon atom with an aromatic nitrogen atom in **11** was examined with the preparation of **19**.



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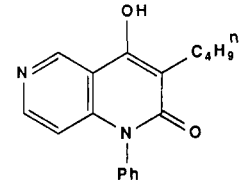

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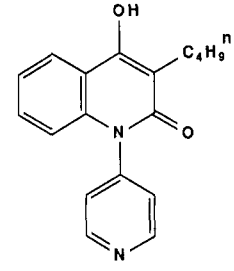

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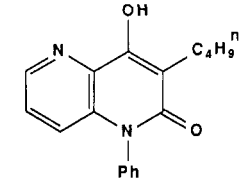

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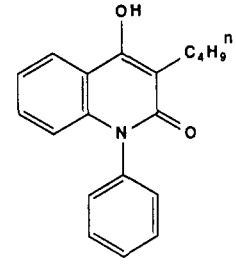
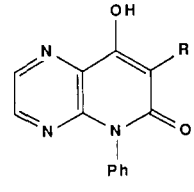


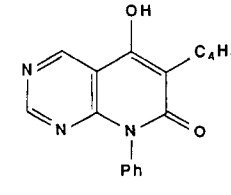
18

Only the pyrazine congeners **19** and **20**, and the tetrahydro analogue **13**, exhibited activity comparable to **11**. Compounds **14**, **15**, **17**, **18**, and **21** were significantly less active than **11** in vitro. In all cases, none of the analogues described above exhibited oral activity comparable to **11** in the allergic bronchospasm model in the guinea pig.



19 R = $C_4H_9^n$

20 R = $CH_2CH{=}C(CH_3)_2$



21

1,8-Naphthyridin-2(1*H*)-one Substitution. Introduction of alkyl or alkoxy substituents at the 6- and/or 7-position of the 1,8-naphthyridin-2(1*H*)-one system re-

(41) Anderson, W. H.; O'Donnell, M. O.; Simko, M.; Welton, A. F. *Br. J. Pharmacol.* **1983**, *78*, 67.

(42) Wong, S. C.; Sasso, S.; Jones, H.; Kaminski, J. J. *J. Med. Chem.* **1984**, *27*, 20.

(43) Augstein, J.; Farmer, J. B.; Lee, T. B.; Sheard, P.; Tattersall, M. L. *Nature (London)* **1973**, *245*, 215.

(44) Fromson, J. M.; Pearson, S.; Bramah, S. *Xenobiotica* **1973**, *3*, 693.

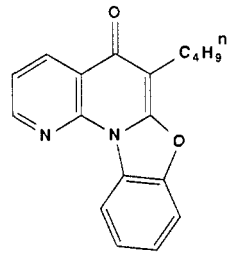
(45) Robertson, D. W.; Katzenellenbogen, J. A.; Long, D. J.; Rurke, E. A.; Katzenellenbogen, B. S. *J. Steroid Biochem.* **1982**, *16*, 1.

(46) Jordan, V. C.; Bain, R. R.; Brown, R. R.; Gosden, B.; Santos, M. A. *Cancer Res.* **1983**, *43*, 1446.

(47) Lyman, S. D.; Jordan, R. C. *Biochem. Pharmacol.* **1985**, *34*, 2787.

sulted in analogues less active than **11** in vitro. Only the 6-hydroxy and 6-bromo substituted analogues, **27** and **28**, respectively, resulted in active antiallergy agents in vitro. However, this in vitro activity did not translate into an orally active entity.

R_1 Substituent. The necessity of the substituent at the 1-position of the 1,8-naphthyridin-2(1*H*)-one to be phenyl in order to maintain antiallergy activity was investigated with the preparation of analogues **34–38**. Only the 1-*n*-hexyl compound, **35**, exhibited significant in vitro antiallergy activity, but was inactive following oral administration. The conformation of the 1-phenyl substituent and its effect on antiallergy activity was investigated with compound **69**. In contrast to other 1-phenyl-substituted 1,8-naphthyridin-2(1*H*)-ones, in which it has been determined by single-crystal X-ray analysis and computational methods that the 1-phenyl substituent is essentially perpendicular to the plane of the 1,8-naphthyridin-2(1*H*)-one ring system (e.g. **115**), the orientation of the phenyl group in the constrained congener **69** must be approximately coplanar with the 1,8-naphthyridin-2(1*H*)-one ring system. Interestingly, **69** is inactive as an antiallergy agent in vitro.



69

Aromatic Substitution. Introduction of either electron-donating or electron-withdrawing substituents into the different positions of the pendant 1-phenyl ring resulted in compounds that exhibited significant antiallergy activity in vitro and in vivo. For example, introduction of a *p*-methoxy substituent into the 1-phenyl ring resulted in compounds **39** and **40**. Both of these analogues exhibited significant in vitro antiallergy activity comparable to **11** but were less active in vivo. The introduction of additional methoxy or other alkoxy substituents in the phenyl ring led to less active analogues in vitro.

Introduction of a *p*-methylthio substitutent at the 3- or 4-position in the phenyl ring resulted in compounds **48** and **52**, which exhibited in vitro antiallergy activity. In contrast to the *p*-methoxy-substituted analogue, the *p*-methylthio-substituted compound, **52**, was inactive in vivo. However, the *m*-methyl-substituted derivative, **48**, was active in vitro and in vivo. Oxidation of the sulfur atom led to analogues **50**, **51**, and **54**, **55**, which were less active antiallergy agents in vitro than there corresponding sulfides, **49** and **53**, respectively.

The presence of a *p*-fluoro substituent in the phenyl ring resulted in compound **60**, which was active in vitro but not in vivo as an antiallergy agent. Interestingly, the O-acetylated analogue **61**, a potential prodrug of **60**, maintained in vitro antiallergy activity and was also orally active in vivo.

R_4 Substituent. Derivatization of the oxygen atom at the 4-position of the 1,8-naphthyridin-2(1*H*)-one ring system, other than acetylation, led to inactive analogues with two exceptions. Compound **121** was active in vitro as an antiallergy agent, but lacked oral activity in vivo, while compound **115** was active both in vitro and in vivo. However, the antiallergy activity of **115** was not maintained after multiple dosing of the test drug.

Table V. Inhibition by **12** of Antigen-Induced Release of LTD_4 from Sensitized Guinea Pig Lung

	release of LTD_4	
addition[d]	LTD_4 production, pmol/g[c]	bioassayable SRS-A, units/g[b]
DMSO vehicle	82	29.6 ± 5.5
12 (10 μM)	25 (70% inhibition)	9.3 ± 3.2[a] (69% inhibition)

[a] $p < 0.05$ compared to the vehicle group by a *t* test for paired comparisons. [b] Mean ± SEM (n = 4 lungs). SRS-A assayed on guinea pig ileum. [c] Ethanol extracts from four separate lungs (with or without **12**) were pooled and separated by reverse-phase HPLC. [d] Compound **12** (10 μM) was added to the lung preparations 12 min before challenge with antigen. The Tyrode's buffer was supplemented with 10 mM cysteine and 10 μM indomethacin.

R_3 Substituent. The antiallergy activity of a significant number of 1,8-naphthyridin-2(1*H*)-ones containing different functional groups at the 3-position (**93–110**) was examined (Table IV). It became apparent after introduction of a considerable number of 3-substituents with widely varying physical and chemical properties that the 3-(2-propenyl) substituent (e.g. analogue **108**) was uniquely effective for imparting enhanced levels of in vitro and in vivo antiallergy activity relative to the prototype **11**. Furthermore, the O-acetylated derivative **12**, a prodrug of **108**, exhibited greater in vivo potency as an antiallergy agent following oral administration, although its in vitro potency relative to **11** may be less.

Further structural modification of 1-phenyl-3-(2-propenyl)-4-acetoxy-1,8-naphthyridin-2(1*H*)-one (**12**) led to the 1-(3′-chlorophenyl)- and 1-(3′-methoxyphenyl)-substituted analogues **87** and **89**, respectively. Both of these analogues exhibited an in vitro and in vivo antiallergy potency comparable to that of **12**.

Mechanism of Action. In view of the unique antiallergy activity exhibited by this series of compounds, some comment on mechanism of action is warranted. As discussed in the introduction to this paper, the 1,8-naphthyridin-2(1*H*)-ones reported are orally active, potent inhibitors of allergic and nonallergic bronchospasm in animal models. The former activity has been attributed to inhibition of the elaboration of sulfidopeptide leukotrienes. In order to understand better the mechanism of action with respect to this series of compounds, some suggestive experimental evidence has been accumulated for our focal compound.

In vitro, in the rat polymorphonuclear leucocyte[48] or in the cloned murine mast cell (MC-9)[49] at a concentration of 50 μM, compound **12** does not inhibit the production of leukotriene products derived from the 5-lipoxygenase pathway of arachidonic acid metabolism. The inhibition of the release of LTD_4 from sensitized guinea pig lung by **12** has been measured by bioassay and quantitatively by measuring the LTD_4 by HPLC (Table V). The close correlation of the inhibition of the release of LTD_4 by both methods of analysis confirms that **12** exerts its pharmacologic effect by inhibiting the release of the sulfidopeptide leukotrienes.

In conclusion, the antiallergy activity of a new class of substituted 1,8-naphthyridin-2(1*H*)-ones has been described. Structure–activity studies in this series led to three compounds, **12**, **87**, and **89**, that exhibited potentially promising antiallergy profiles. Of these analogues, 1-phenyl-3-(2-propenyl)-4-acetoxy-1,8-naphthyridin-2-

(48) Myers, R. F.; Siegel, M. I. *Biochem. Biophys. Res. Commun.* **1983**, *112*, 586.
(49) Musch, M.; Bryant, R. W.; Cosolluela, C.; Myers, R. F.; Siegel, M. I. *Prostaglandins* **1985**, *29*, 405.

(1*H*)-one, Sch 33303 (**12**), was selected for preclinical development as an antiallergy drug.

Experimental Section

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. The NMR spectra were recorded with a Varian CFT-20 or a Varian XL-400 spectrometer, IR spectra were recorded with a Perkin-Elmer 221 spectrophotometer, and mass spectra were obtained with a Varian MAT CH5 spectrometer. Microanalyses were performed by the Physical-Analytical Service Department of the Schering-Plough Corp. Leukotrienes B_4, C_4, and D_4 were obtained from Professor E. J. Corey, Harvard University. [^{3}H]LTD$_4$ and LTC$_4$ radioimmunoassay kit were obtained from New England Nuclear Corp.

Chemistry. Substituted Nicotinic Acids and Derivatives (1). The substituted nicotinic acids and esters described in Table I were either commercially available from the Aldrich Chemical Co. or their preparation has been reported previously.[18-23]

Substituted Amines (2). The substituted amines (**2**) needed were commercially available from the Aldrich Chemical Co. and Polysciences Incorporated.

Substituted Pyridines (3) and Congeners. By use of the procedures described by Kermack and Weatherhead[24] and Nantka-Namirsky,[25] fusion of substituted 2-chloronicotinic acid (**1**), method A, or a substituted 2-chloronicotinic ester (**1**), method B, with an appropriately substituted amine (**2**) gave the corresponding substituted pyridines (**3a–3aa** and **3bb–3ccc**) as described in Table II.

Method C. Methyl 2-(*o*-methoxyanilino)nicotinate (3gg). To 40.0 g (0.16 mol) of 2-(*o*-methoxyanilino)nicotinic acid (**3**) and 17.0 g (0.17 mol) of triethylamine dissolved in 350 mL acetone was added dropwise with stirring at 0 °C 13.5 g (0.18 mol) of chloroacetonitrile. The solution was heated under reflux for 18 h and filtered while hot. Upon cooling, the filtrate was concentrated under reduced pressure. The solid obtained was thoroughly washed with water and dried in vacuo to give 44.2 g (0.16 mol), 100%, of cyanomethyl 2-(*o*-methoxyanilino)nicotinate, mp 136–138 °C, which was used without further purification.

A solution of 43.5 g (0.15 mol) cyanomethyl 2-(*o*-methoxyanilino)nicotinate and 3.0 g (0.03 mol) of triethylamine dissolved in 450 mL of methanol was heated under reflux for 6 h. Upon cooling, the solids that formed were isolated by filtration and washed with cold methanol. Recrystallization from methanol gave 36.1 g (0.14 mol), 91%, of methyl 2-(*o*-methoxyanilino)nicotinate (**3gg**): mp 118–120 °C. Anal. ($C_{14}H_{14}N_2O_3$) C, H, N.

By use of the procedure described above (method C), substituted pyridines (**3hh–ggg**) were prepared as described in Table II. Congeners **5** and **7** were also prepared from their respective acids by using method C.

Methyl 2-Anilino-5-hydroxynicotinate (3hhh). To 8.0 g (0.035 mol) of methyl 2-anilinonicotinate (**3bb**) dissolved in 30 mL of acetic acid was added 15 mL of 30% hydrogen peroxide. The solution was heated at 100 °C for an additional 16 h. Upon cooling, the solution was poured into ice (100 g) and basified by the addition of ammonium hydroxide. The basic solution was extracted with dichloromethane (4 × 300 mL), and the combined extracts were dried ($MgSO_4$). Following filtration, the dichloromethane was removed under reduced pressure to give 6.2 g of an oil. Chromatography on silica gel, eluting with ethyl acetate/hexane, 25/75 by volume, gave after recrystallization from ether/hexane 1.2 g (0.005 mol), 14%, of methyl 2-anilino-5-hydroxynicotinate (**3hhh**): mp 154–156 °C. Anal. ($C_{13}H_{12}N_2O_3$) C, H, N.

2-Anilino-3-carbomethoxyquinoline (3iii). To a mixture of 11 g of palladium on carbon (5%) in 120 mL of *p*-cymene under an atmosphere of carbon dioxide was added 12.0 g (0.043 mol) of 2-anilino-3-carbomethoxy-5,6,7,8-tetrahydroquinoline (**3ggg**) dissolved in 30 mL of *p*-cymene. The mixture was heated under reflux for 24 h. Upon cooling, the catalyst was removed by filtration and thoroughly washed with toluene. The filtrate was concentrated under reduced pressure to give a yellow solid. Recrystallization from hexane gave 9.5 g (0.034 mol), 80%, of 2-anilino-3-carbomethoxyquinoline (**3iii**): mp 100–101 °C. Anal. ($C_{17}H_{14}N_2O_2$) C, H, N.

***N*-Acylpyridines (4). Method D. 2-(*N*-Acetylanilino)-3-carbomethoxypyridine.** A solution of 110 g (0.48 mol) of methyl 2-anilinonicotinate (**3bb**) dissolved in 700 mL of acetic anhydride under a nitrogen atmosphere was heated under reflux for 24 h. Approximately 500 mL of acetic anhydride was removed by distillation at atmospheric pressure, and the residue was added to ice (800 g). The mixture was stirred for 0.5 h. The solids that formed were isolated by filtration, washed thoroughly with water and dried in vacuo. Recrystallization from isopropyl acetate gave 110.7 g (0.41 mol), 85%, of 2-(*N*-acetylanilino)-3-carbomethoxypyridine (**4a**): mp 119–120 °C. Anal. ($C_{15}H_{14}N_2O_3$) C, H, N.

By use of the procedure described above (method D), treatment of a substituted pyridine (**3**) with an appropriate acylating agent gave the corresponding *N*-acylpyridine (**4b–m**) described in Table III.

Substituted 1,8-Naphthyridin-2(1*H*)-ones. Method E. 1-Phenyl-3-*n*-butyl-4-hydroxy-1,8-naphthyridin-2(1*H*)-one (11). A mixture containing 182.4 g (0.80 mol) of methyl 2-anilinonicotinate (**3bb**) and 792 mL of ethyl caproate was stirred under a nitrogen atmosphere while 184.7 g (1.6 mol) of potassium *tert*-butoxide (87%) was added in portions over 0.25 h. The mixture was heated under reflux for 4 h. Upon cooling, 500 mL of toluene was added, and the mixture was filtered. The solid isolated by filtration was thoroughly washed with toluene and air-dried, 325.4 g. The solid was dissolved in 550 mL of water, the insolubles were removed by filtration, and the filtrate was acidified to pH 2 by the addition of concentrated hydrochloric acid. The solid that formed was isolated by filtration, thoroughly washed with ether, and air-dried, 230.3 g. Recrystallization from ethanol gave 211.7 g (0.72 mol), 80%, of 1-phenyl-3-*n*-butyl-4-hydroxy-1,8-naphthyridin-2(1*H*)-one (**11**): mp 235–237 °C; ^{1}H NMR (DMSO-d_6) δ 8.4 (dd, 1 H), 8.3 (dd, 1 H), 7.2 (dd, 1 H), 7.4–7.1 (aromatic, 5 H), 2.6 (m, 2 H), 1.4 (m, 4 H), and 0.9 (t, 3 H).

1-Phenyl-3-*n*-butyl-4-hydroxy-1,8-naphthyridin-2(1*H*)-one (**11**), 208.7 g (0.71 mol), was neutralized by the addition of 700 mL of 1 N sodium hydroxide (0.70 mol). The suspension was diluted with an additional 1800 mL water and stirred overnight. The solids remaining were removed by filtration (2.6 g), and the filtrate was lyophilized to give 221.1 g (0.67 mol), 95%, of the sodium salt of 1-phenyl-3-*n*-butyl-4-hydroxy-1,8-naphthyridin-2(1*H*)-one (**11**): mp 245–262 °C. Anal. ($C_{18}H_{17}N_2Na \cdot {}^3/_4H_2O$) C, H, N, Na.

The procedure described above, method E, with or without the salt formation step, was used to prepare the substituted 1,8-naphthyridin-2(1*H*)-ones **13**, **14**, **17**, **19**, **21–25**, **27–29**, **34–38**, **42–45**, **47**, **48**, **52**, **56**, **57**, **63**, **64**, **68**, **73**, **74**, **95**, **97–101**, **105**, **109**, and **110** described in Table IV.

Method F. 1-Phenyl-4-hydroxy-1,8-naphthyridin-2-(1*H*)-one (93). To 30.0 g (0.11 mol) of methyl 2-(*N*-acetylanilino)nicotinate (**4a**) dissolved in 1 L of xylene was added a suspension of 27.6 g (0.25 mol) of potassium *tert*-butoxide (87%) in 30 mL of xylene. The mixture was heated under reflux with stirring for 4 h. Upon cooling, 300 mL of water was added, and the layers were separated. The aqueous layer was acidified to pH 6 by the addition of glacial acetic acid. The solids that were formed were isolated by filtration, washed thoroughly with water, and air-dried. Recrystallization from methanol gave 24.6 g (0.11 mol), 93%, of 1-phenyl-4-hydroxy-1,8-naphthyridin-2(1*H*)-one (**93**): mp 309–310 °C. Anal. ($C_{14}H_{10}N_2O_2$) C, H, N.

By use of the procedure described above, method F, the substituted 1,8-naphthyridin-2(1*H*)-ones **11**, **39**, **41**, **60**, **67**, **70–72**, **75**, **94**, and **96** were prepared (Table IV).

Method G. 1-Phenyl-4-(allyloxy)-1,8-naphthyridin-2-(1*H*)-one (76). A mixture of 62.0 g (0.26 mol), of 1-phenyl-4-hydroxy-1,8-napthyridin-2(1*H*)-one (**93**) and 39.6 g (0.29 mol) of potassium carbonate in 1800 mL of acetone was heated under reflux with stirring for 0.5 h. Upon cooling, 37.5 g (0.31 mol) of allyl bromide was added dropwise with stirring. The mixture was again heated under reflux with stirring for 24 h. Upon cooling, the volatiles were removed under reduced pressure. The residue obtained was dissolved in 600 mL of chloroform and washed with 500 mL of water, 100 mL of 1 N sodium hydroxide, and 100 mL of water. The chloroform solution was dried ($MgSO_4$). Following filtration, the chloroform was removed under reduced pressure to give a solid, 91.5 g. Trituration with isopropyl ether (4 × 300 mL) followed by recrystallization from methanol gave 34.2 g (0.12 mol), 47%, of 1-phenyl-4-(allyloxy)-1,8-naphthyridin-2(1*H*)-one (**76**): mp 176–177 °C. Anal. ($C_{17}H_{14}N_2O_2$) C, H, N.

By use of the procedure described above (method G), the substituted 1,8-naphthyridin-2(1*H*)-ones **31**, **76–82**, **111–113**, and **115–121** were prepared as described in Table IV.

Method H. 1-Phenyl-3-(2-propenyl)-4-acetoxy-1,8-naphthyridin-2(1*H*)-one (12). 1-Phenyl-4-(allyloxy)-1,8-naphthyridin-2(1*H*)-one (**76**), 33.9 g (0.12 mol), was dissolved in 31.5 g (0.31 mol), of acetic anhydride, and the solution was heated under reflux for 4 h. Upon cooling, the solids that formed were isolated by filtration and triturated with isopropyl ether (100 mL). Recrystallization from ethanol gave 20.6 g (0.06 mol), 52%, of 1-phenyl-3-(2-propenyl)-4-acetoxy-1,8-naphthyridin-2(1*H*)-one (**12**): mp 195–196 °C; ^{1}H NMR ($CDCl_3$) δ 8.4 (dd, 1 H), 7.8 (dd, 1 H), 7.1 (dd, 1 H), 7.5–7.3 (aromatic, 5 H), 5.9 (m, 1 H), 5.2–5.0 (m, 2 H), 3.4 (d, 3 H), and 2.5 (s, 3 H). Anal. ($C_{19}H_{16}N_2O_3$) C, H, N.

By use of the procedure described above (method H), the substituted 1,8-naphthyridin-2(1*H*)-ones **32** and **83–88** were prepared (Table IV).

Method I. 1-Phenyl-3-(2-propenyl)-4-hydroxy-1,8-naphthyridin-2(1*H*)-one (108). To 135 mL of ethanol containing 95 mL of 1 N sodium hydroxide (0.095 mol) was added 15.0 g (0.047 mol) of 1-phenyl-3-(2-propenyl)-4-acetoxy-1,8-naphthyridin-2(1*H*)-one (**12**), and the solution was stirred at ambient temperature overnight. Water (50 mL) was added, and the solution was acidified to pH 2 by the addition of 15% hydrogen chloride. The solid that formed was isolated by filtration, washed thoroughly with water, and air-dried, 13.2 g. Recrystallization from chloroform gave 12.1 g (0.44 mol), 93%, of 1-phenyl-3-(2-propenyl)-4-hydroxy-1,8-naphthyridin-2(1*H*)-one (**108**): mp 251–252 °C. Anal. ($C_{17}H_{14}N_2O_2$) C, H, N.

By use of the procedure described above (method I), the substituted 1,8-naphthyridin-2(1*H*)-ones **89–92**, **108**, and **109** were prepared (Table IV).

Method J. 1-(*p*-Methoxyphenyl)-3-*n*-butyl-4-acetoxy-1,8-naphthyridin-2(1*H*)-one (40). A solution of 1.5 g (0.005 mol) of 1-(*p*-methoxyphenyl)-3-*n*-butyl-4-acetoxy-1,8-naphthyridin-2-(1*H*)-one (**39**) dissolved in 7 mL of acetic anhydride and 7 mL of benzene was heated under reflux for 24 h. Upon cooling, the volatiles were removed under reduced pressure. The solid obtained was washed thoroughly with water and air-dried, 1.7 g. Recrystallization from ethyl acetate gave 1.5 g (0.004 mol), 89%, of 1-(*p*-methoxyphenyl)-3-*n*-butyl-4-acetoxy-1,8-naphthyridin-2-(1*H*)-one (**40**): mp 184–185 °C. Anal. ($C_{21}H_{22}N_2O_4$) C, H, N.

By use of the procedure described above (method J), the substituted 1,8-naphthyridin-2(1*H*)-ones **49**, **53**, **61**, and **66** were prepared (Table IV).

1-Phenyl-3-*n*-butyl-1,6-naphthyridin-2(1*H*)-one (15) and 1-(4-Pyridyl)-3-*n*-butyl-4-hydroxy-2(1*H*)-quinolone (16). A mixture of 3.2 g (0.019 mol) of 4-anilinopyridine (**6**) and 10.8 g (0.021 mol) of bis-(2,4,6-trichlorophenyl) 2-*n*-butylmalonate[32] in 15 mL of toluene was heated in a nitrogen atmosphere to obtain a homogeneous solution (240 °C) with the distillation of solvent. The mixture was heated at 250 °C for 0.75 h. Upon cooling, 400 mL of ether was added, and the ethereal solution was extracted with 125 mL of 0.5 N sodium hydroxide. The basic aqueous solution was acidified to pH 6 by the addition of concentrated hydrochloric acid and extracted with ether and dichloromethane. The extracts were combined and dried (Na_2SO_4). Following filtration, the solution was concentrated to a volume of 50 mL. Ethanolic hydrogen chloride (10%), 300 mL, was added followed by the addition of 300 mL of ether. The solid that formed was isolated by filtration, 2.9 g. Recrystallization from ethanol/ether gave 1.25 g of **15**·HCl: mp 295–300 °C. Neutralization and recrystallization from acetonitrile gave 0.9 g (0.003 mol), 16%, of 1-phenyl-3-*n*-butyl-4-hydroxy-1,6-naphthyridin-2(1*H*)-one (**15**): mp 198–200 °C. Anal. ($C_{18}H_{18}N_2O_2$) C, H, N.

The filtrate that produced **15**·HCl was concentrated under reduced pressure. The residue obtained was dissolved in 14 mL of 1 N sodium hydroxide and 14 mL of water. The solid that separated was isolated by filtration, 0.95 g. Recrystallization from acetonitrile gave 0.82 g (0.003 mol), 14%, of 1-(4-pyridyl)-3-*n*-butyl-4-hydroxy-2(1*H*)-quinolone (**16**): mp 234–236 °C. Anal. ($C_{18}H_{18}N_2O_2$) C, H, N.

8-Hydroxy-7-(3-methyl-2-butenyl)-5-phenylpyrido[2,3-*b*]pyrazin-6(5*H*)-one (20). A mixture containing 91.2 g (0.4 mol) of diethyl (3-methyl-2-butenyl)malonate,[33] 29.4 g (0.5 mol) of sodium chloride, and 27.0 g (1.5 mol) of water in 600 mL of dimethyl sulfoxide was heated under reflux with vigorous stirring for 20 h. The reaction mixture was poured onto 1 L of ice, and 600 mL of ether was added. The layers were separated, and the aqueous layer was extracted with ether (3 × 300 mL). The ether extracts were combined, washed with water (1 × 200 mL), and dried ($MgSO_4$). Following filtration, the ether was removed under reduced pressure to give an oil, 75 g. Distillation under reduced pressure gave 49.8 g (0.32 mol), 80%, of ethyl 5-methylhex-4-enoate: bp 110–118 °C (60 mmHg).

2-Anilino-3-carbomethoxypyrazine (**9**), 2.29 g (0.01 mol), was reacted with ethyl 5-methylhex-4-enoate, by using method E, to give after recrystallization from isopropyl ether, 2.6 g (0.0085 mol), 85%, of 8-hydroxy-7-(3-methyl-2-butenyl)-5-phenylpyrido[2,3-*b*]pyrazin-6(5*H*)-one (**20**): mp 172–173 °C. Anal. ($C_{18}H_{17}N_3O_2$) C, H, N.

1-Phenyl-4-hydroxy-6-methoxy-1,8-naphthyridin-2(1*H*)-one (30). Sodium, 1.1 g (0.048 mol), was dissolved in 13 mL of methanol, and the resulting solution was diluted with 13 mL of *N*,*N*-dimethylformamide. Cuprous iodide, 1.2 g (0.006 mol), and 1-phenyl-6-bromo-1,8-napthyridin-2(1*H*)-one (**29**), 4.0 g (0.012 mol), was added to the solution above, and the mixture was heated under reflux for 3 h. Upon cooling, the insolubles were removed by filtration and thoroughly washed with methanol. The methanol filtrates were concentrated under reduced pressure. The residue obtained was dissolved in 70 mL of water, and the solution was acidified to pH 3 by the addition of glacial acetic acid. The solid that formed was isolated by filtration. Recrystallization from methanol gave 2.1 g (0.008 mole, 62%, of 1-phenyl-6-methoxy-1,8-napthyridin-2(1*H*)-one (**30**): mp 285–287 °C. Anal. ($C_{15}H_{12}N_2O_3$) C, H, N.

1-Phenyl-3-(2-propenyl)-4,6-dihydroxy-1,8-naphthyridin-2(1*H*)-one (33). To a stirred suspension of 2.8 g (0.07 mol) of sodium hydride in mineral oil (60%) in 70 mL of *N*,*N*-dimethylformamide was added dropwise over 0.25 h a solution of 4.7 mL (0.063 mol) of ethyl mercaptan in 70 mL of *N*,*N*-dimethylformamide. The suspension was stirred for 0.5 h, and a solution of 4.9 g (0.014 mol) of 1-phenyl-3-(2-propenyl)-4-acetoxy-6-methoxy-1,8-naphthyridin-2(1*H*)-one (**32**) in 70 mL of *N*,*N*-dimethylformamide was added dropwise over 0.25 h. The mixture was heated under reflux for 3 h. Upon cooling, the mixture was poured onto ice (100 g) and extracted with ether (3 × 100 mL). The aqueous layer was acidified to pH 2 by the addition of hydrochloric acid (15%) and extracted with dichloromethane (3 × 200 mL). The extracts were combined and dried (Na_2SO_4). Following filtration, the solvent was removed under reduced pressure to give a solid that was triturated with dichloromethane (100 mL). Recrystallization from acetonitrile gave 2.9 g (0.01 mol), 70%, of 1-phenyl-3-(2-propenyl)-4,6-dihydroxy-1,8-naphthyridin-2(1*H*)-one (**33**): mp 241–243 °C. Anal. ($C_{17}H_{14}N_2O_3$) C, H, N.

1-(*p*-Hydroxyphenyl)-3-*n*-butyl-4-hydroxy-1,8-naphthyridin-2(1*H*)-one (46). To a mixture of 5 mL of glacial acetic acid and 15 mL of hydrobromic acid (48%) was added 1.0 g (0.003 mol) of 1-(*p*-methoxyphenyl)-3-*n*-butyl-4-hydroxy-1,8-naphthyridin-2(1*H*)-one (**39**), and the solution was heated under reflux for 24 h. The reaction mixture was concentrated under reduced pressure, and the residue obtained was dissolved in sodium hydroxide (10%) and neutralized to pH 7. The solid that formed was isolated by filtration, washed thoroughly with water, and air-dried. Recrystallization from acetonitrile gave 0.55 g (0.0017 mol), 57%, of 1-(*p*-hydroxyphenyl)-3-*n*-butyl-4-hydroxy-1,8-naphthyridin-2(1*H*)-one (**46**): mp 290–292 °C. Anal. ($C_{18}H_{18}N_2O_3$) C, H, N.

1-[3-(Methylsulfinyl)phenyl]-3-*n*-butyl-4-acetoxy-1,8-naphthyridin-2(1*H*)-one (50). To a solution of 4.2 g (0.011 mol) of 1-[3-(methylthio)phenyl]-3-*n*-butyl-4-acetoxy-1,8-naphthyridin-2(1*H*)-one (**49**) in 80 mL of dichloromethane was added 2.52 g (0.012 mol) of *m*-chloroperbenzoic acid (80%) in portions at 0–5 °C. The solution was stirred at 0 °C for 0.5 h and at ambient temperature for 4 h. The dichloromethane solution was washed with 80 mL of 0.5 N sodium hydroxide and 80 mL of water and dried ($MgSO_4$). Following filtration, the dichloromethane was removed under reduced pressure to give an oil that crystallized on treatment with ethyl acetate. Recrystallization from ethyl acetate/hexane gave 3.2 g (0.008 mol), 72%, of 1-

[3-(methylsulfinyl)phenyl]-3-*n*-butyl-4-acetoxy-1,8-naphthyridin-2(1*H*)-one (**50**): mp 166–168 °C. Anal. ($C_{21}H_{22}N_2O_4S$) C, H, N.

1-[3-(Methylsulfonyl)phenyl]-3-*n*-butyl-4-acetoxy-1,8-naphthyridin-2(1*H*)-one (51). With use of the procedure described for the preparation of 1-[3-(methylsulfinyl)phenyl]-3-*n*-butyl-4-acetoxy-1,8-naphthyridin-2(1*H*)-one (**50**), but with use of 2 equiv of *m*-chloroperbenzoic acid, there was obtained 2.3 g (0.006 mol), 93%, of 1-[3-(methylsulfonyl)phenyl]-3-*n*-butyl-4-acetoxy-1,8-naphthyridin-2(1*H*)-one (**51**): mp 201–202 °C. Anal. ($C_{21}H_{22}N_2O_5S$) C, H, N.

1-[4-(Methylsulfinyl)phenyl]-3-*n*-butyl-4-acetoxy-1,8-naphthyridin-2(1*H*)-one (54): With use of the procedure described for the preparation of 1-[3-(methylsulfinyl)phenyl]-3-*n*-butyl-4-acetoxy-1,8-naphthyridin-2(1*H*)-one (**50**), treatment of 1-[4-(methylthio)phenyl]-3-*n*-butyl-4-acetoxy-1,8-naphthyridin-2(1*H*)-one (**53**) with 1 equiv of *m*-chloroperbenzoic acid gave 2.0 g (0.005 mol), 50%, of 1-[4-(methylsulfinyl)phenyl]-3-*n*-butyl-4-acetoxy-1,8-naphthyridin-2(1*H*)-one (**55**): mp 185–188 °C. Anal. ($C_{21}H_{22}N_2O_4S$) C, H, N.

1-[4-(Methylsulfonyl)phenyl]-3-*n*-butyl-4-acetoxy-1,8-naphthyridin-2(1*H*)-one (55): With use of the procedure described for the preparation of 1-[3-(methylsulfonyl)phenyl]-3-*n*-butyl-4-acetoxy-1,8-naphthyridin-2(1*H*)-one (**51**), treatment of 1-[4-methylthio)phenyl]-3-*n*-butyl-4-acetoxy-1,8-naphthyridin-2(1*H*)-one (**53**) with 2 equiv of *m*-chloroperbenzoic acid gave 2.0 g (0.005 mol), 20%, of 1-[4-(methylsulfonyl)phenyl]-3-*n*-butyl-4-acetoxy-1,8-naphthyridin-2(1*H*)-one (**55**): mp 185–188 °C. Anal. ($C_{21}H_{22}O_5N_2S$) C, H, N.

1-(4-Acetylphenyl)-3-*n*-butyl-4-hydroxy-1,8-naphthyridin-2(1*H*)-one (58). A mixture of 22.2 g (0.082 mol) of methyl 2-(4-acetylanilino)nicotinate (**3xx**), 50 mL of ethylene glycol, and 1 g of *p*-toluenesulfonic acid in 350 mL of toluene was heated under reflux for 5 h with azeotropic removal of water. The mixture was poured onto ice (100 g), and 100 mL of saturated sodium bicarbonate was added. The solution was extracted with ethyl acetate (3 × 100 mL), and the extracts were combined and dried ($MgSO_4$). Following filtration, the ethyl acetate was removed under reduced pressure to give an oil. Crystallization of the oil occurred on treatment with hexane to give 19.9 g (0.063 mol), 77%, of methyl 2-[4-[1,1-(ethylenedioxy)ethyl]anilino]nicotinate, mp 75–77 °C, which was used without further purification.

Methyl 2-[4-[1,1-(ethylenedioxy)ethyl]anilino]nicotinate, 1.4 g (0.005 mol), was reacted with ethyl caproate by using method E, to give 1.3 g (0.0034 mol), 76%, of 1-[4-[1,1-(ethylenedioxy)-ethyl]phenyl]-3-*n*-butyl-4-hydroxy-1,8-naphthyridin-2(1*H*)-one, mp 281–283 °C, which was used without further purification.

A mixture of 1.3 g (0.0034 mol) of 1-[4-[1,1-(ethylenedioxy)-ethyl]phenyl]-3-*n*-butyl-4-hydroxy-1,8-naphthyridin-2(1*H*)-one in 150 mL of acetone and 150 mL of water containing 2 mL of concentrated hydrochloric acid was stirred at ambient temperature for 24 h. The volatiles were removed under reduced pressure, and the solution remaining was neutralized to pH 5 by the addition of dilute sodium hydroxide (10%). The solid that formed was isolated by filtration, dissolved in ethyl acetate, and dried ($MgSO_4$). Following filtration, the ethyl acetate was removed under reduced pressure. Recrystallization from ethyl acetate gave 0.9 g (0.0027 mol), 70%, of 1-(4-acetylphenyl)-3-*n*-butyl-4-hydroxy-1,8-naphthyridin-2(1*H*)-one (**58**): mp 267–269 °C. Anal. ($C_{20}H_{20}N_2O_3$) C, H, N.

1-[4-(Hydroxyethyl)phenyl]-3-*n*-butyl-4-hydroxy-1,8-naphthyridin-2(1*H*)one (59). To 3.4 g (0.01 mol) of 1-(4-acetylphenyl)-3-*n*-butyl-4-hydroxy-1,8-naphthyridin-2(1*H*)-one (**58**) suspended in 100 mL of methanol at 0 °C was added in portions with stirring 2.0 g (0.053 mol) of sodium borohydride. The mixture was stirred at 0 °C for 1.5 h and poured onto ice and water (500 g), and the solution was adjusted to pH 5 by the addition of concentrated hydrochloric acid. The solid that formed was isolated by filtration and air-dried, 3.1 g. Recrystallization from methanol gave 2.1 g (0.0062 mol), 62%, of 1-[4-(hydroxyethyl)phenyl]-3-*n*-butyl-4-hydroxy-1,8-naphthyridin-2(1*H*)-one (**59**): mp 258–259 °C. Anal. ($C_{20}H_{22}N_2O_3$) C, H, N.

1-(3-Carboxy-4-hydroxyphenyl)-3-*n*-butyl-4-hydroxy-1,8-naphthyridin-2(1*H*)-one (65). 1-(3-Carboethoxy-4-hydroxyphenyl)-3-*n*-butyl-4-hydroxy-1,8-naphthyridin-2(1*H*)-one (**64**), 1.6 g (0.004 mol), dissolved in 10 mL of ethanol and 30 mL of 1 N potassium hydroxide was heated under reflux for 24 h. Upon cooling, the volatiles were removed under reduced pressure, and the remaining solution was acidified to pH 3 by the addition of hydrochloric acid (10%). The solid that formed was isolated by filtration. Recrystallization from ethanol/isopropyl ether gave 1.0 g (0.0028 mol), 70%, of 1-(3-carboxy-4-hydroxyphenyl)-3-*n*-butyl-4-hydroxy-1,8-naphthyridin-2(1*H*)-one (**65**): mp 274–276 °C. Anal. ($C_{19}H_{18}N_2O_5$) C, H, N.

6-*n*-Butyl-5*H*-benzoxazolo[3,2-*a*][1,8]naphthyridin-5-one (69). 2-Chloronicotinic acid (**1a**), 31.5 g (0.2 mol), was reacted with *o*-hydroxyaniline (**2aa**), 43.6 g (0.4 mol), by method A, to give 42.0 g (0.18 mol), 90%, of (*o*-hydroxyanilino)nicotinic acid, mp 230–232 °C, which was used without further purification. Following the procedure described by Kim,[34] 10.0 g (0.044 mol) of (*o*-hydroxyanilino)nicotinic acid was treated with hexanoic anhydride (100 mL) to give after recrystallization from ether/hexane 9.1 g (0.031 mol), 72%, 6-*n*-butyl-5*H*-benzoxazolo[3,2-*a*][1,8]naphthyridin-5-one 6-*n*-butyl-5*H*-benzooxaolo[3,2-*a*]-[1,8]naphthyridin-5-one (**69**): mp 127–130 °C. Anal. ($C_{18}H_{16}N_2O_2$) C, H, N.

1-Phenyl-3-[3,3-(ethylenedioxy)butyl]-4-hydroxy-1,8-naphthyridin-2(1*H*)-one (102). A mixture of 15 g of ethyl levulinate, 30 mL of ethylene glycol and 0.5 g *p*-toluenesulfonic acid in 300 mL of toluene was heated under reflux for 5 h with azeotropic removal of water. The mixture was poured onto ice (100 g), and 100 mL of saturated sodium bicarbonate was added. The solution was extracted with ethyl acetate (3 × 100 mL), and the extracts were combined and dried ($MgSO_4$). Following filtration, the ethyl acetate was removed under reduced pressure to give an oil. Distillation in vacuo gave 10.6 g (0.052 mol), 55%, of ethyl 5,5-(ethylenedioxy)levulinate, bp 76–82 °C (0.1 mmHg), which was used without further purification.

Methyl 2-anilinonicotinate (**3bb**), 4.6 g (0.02 mol), was reacted with 8.3 g (0.04 mol) of ethyl 5,5-(ethylenedioxy)levulinate, by using method E, to give after recrystallization from ethyl acetate, 3.2 g (0.009 mol), 45%, of 1-phenyl-3-[3,2-(ethylenedioxy)butyl]-4-hydroxy-1,8-naphthyridin-2(1*H*)-one (**102**): mp 180–182 °C. Anal. ($C_{20}H_{20}N_2O_4$) C, H, N.

1-Phenyl-3-(3-oxobutyl)-4-hydroxy-1,8-naphthyridin-2(1*H*)-one (103). A mixture of 2.5 g (0.007 mol) of 1-phenyl-3-[3,2-(ethylenedioxy)butyl]-4-hydroxy-1,8-naphthyridin-2(1*H*)-one (**102**) in 100 mL of dimethoxyethane and 100 mL water containing 1 mL of concentrated hydrochloric acid was stirred at ambient temperature for 24 h. The volatiles were removed under reduced pressure, and the solution remaining was neutralized to pH 5 by the addition of dilute sodium hydroxide (10%). The solid that formed was isolated by filtration. Recrystallization from methanol/ether gave 1.7 g (0.006 mol), 86%, of 1-phenyl-3-(3-oxobutyl)-4-hydroxy-1,8-naphthyridin-2(1*H*)-one (**103**): mp 182–184 °C. Anal. ($C_{18}H_{16}N_2O_3$) C, H, N.

1-Phenyl-3-(3-hydroxybutyl)-4-hydroxy-1,8-naphthyridin-2(1*H*)-one (104). With use of the procedure described for the preparation of compound **59**, treatment of 1-phenyl-3-(3-oxobutyl)-4-hydroxy-1,8-naphthyridin-2(1*H*)-one (**103**) with sodium borohydride gave 2.0 g (0.006 mol), 53%, of 1-phenyl-3-(3-hydroxybutyl)-4-hydroxy-1,8-naphthyridin-2(1*H*)-one (**104**): mp 234–235 °C. Anal. ($C_{18}H_{18}N_2O_3$) C, H, N.

1-Phenyl-3-(2-pyridylethyl)-4-hydroxy-1,8-naphthyridin-2(1*H*)-one (106). 4-(2-Pyridyl)butyric acid[35] was esterified to produce ethyl 4-(2-pyridyl)butyrate, bp 85–86 °C (2 mmHg), which was used without further purification. Methyl 2-anilinonicotinate (**3bb**), 8.0 g (0.035 mol), was reacted with 40.0 g (0.21 mol) of ethyl 4-(2-pyridyl)butyrate, by using method E, to give after recrystallization from ethanol, 10.3 g (0.03 mol), 86%, of 1-phenyl-3-(2-pyridylethyl)-4-hydroxy-1,8-naphthyridin-2(1*H*)-one (**106**): mp 255–257 °C dec. Anal. ($C_{21}H_{17}N_3O_2$) C, H, N.

1-Phenyl-3-[2-(*N*-methylpiperidyl)ethyl]-4-acetoxy-1,8-naphthyridin-2(1*H*)-one (107). Compound **106**, 5.6 g (0.016 mol), was reacted with 35 mL of acetic anhydride, by using method J, to produce after recrystallization from isopropyl acetate, 4.6 g (0.012 mol), 75%, of 1-phenyl-3-(2-pyridylethyl)-4-acetoxy-1,8-naphthyridin-2(1*H*)-one, mp 173–174 °C, that was used without further purification.

1-Phenyl-3-(2-pyridylethyl)-4-acetoxy-1,8-naphthyridin-2-(1*H*)-one, 2.0 g (0.005 mol), and 0.7 g (0.005 mol) of dimethyl sulfate dissolved in 30 mL of benzene was heated under reflux

for 1.5 h. The solid that formed was isolated by filtration and washed with benzene (1 × 5 mL). Trituration with ether (3 × 10 mL) gave 2.2 g (0.0043 mol), 86%, of 1-phenyl]-3-(2-*N*-methylpyridinio-4-acetoxy-1,8-naphthyridin-2(1*H*)-one methyl sulfate, mp 80–105 °C, which was used without further purification.

1-Phenyl-3-(2-*N*-methylpyridinio)-4-acetoxy-1,8-naphthyridin-2(1*H*)-one methyl sulfate, 2.2 g (0.0043 mol), dissolved in 50 mL of ethanol, was hydrogenated over platinum oxide (0.1 g) at 60 psi until the theoretical amount of hydrogen was consumed. The mixture was filtered and the catalyst was thoroughly washed with ethanol. The filtrates were combined, and the ethanol was removed under reduced pressure. The residue obtained was dissolved in 20 mL of water and basified with potassium carbonate. The basic solution was extracted with ethyl acetate and chloroform. The extracts were combined and dried (Na_2SO_4). Following filtration, the solvent was removed under reduced pressure to give a solid. Recrystallization from acetonitrile gave 0.61 g (0.0015 mol), 35%, of 1-phenyl-3-[2-(*N*-methylpiperidyl)ethyl]-4-acetoxy-1,8-naphthyridin-2(1*H*)one (**107**): mp 196–197 °C. Anal. ($C_{24}H_{27}N_3O_3$) C, H, N.

1-Phenyl-3-*n*-butyl-4-[(2,3-dihydroxypropyl)oxy]-1,8-naphthyridin-2(1*H*)-one (114). With use of the procedure described for the deketalization of compound **102**, treatment of compound **113** with ethanolic hydrogen chloride gave 1.8 g (0.0048 mol), 86%, of 1-phenyl-3-*n*-butyl-4-[(2,3-dihydroxypropyl)-oxy]-1,8-naphthyridin-2(1*H*)-one (**114**): mp 162–163 °C. Anal. ($C_{21}H_{24}N_2O_4$) C, H, N.

X-ray Crystal Analysis of 1-Phenyl-3-*n*-butyl-4-(2-hydroxyethoxy)-1,8-naphthyridin-2(1*H*)-one (115). Crystal Data: $C_{20}H_{22}N_2O_3$, M_r 338.41, monoclinic, a = 9.643 (2) Å, b = 22.932 (6) Å, c = 8.664 (1) Å, β = 112.44 (1)°, V = 1770.8 Å^3, Z = 4, d_{calcd} = 1.269 g cm^{-3}, μ(Cu Kα radiation, λ = 1.5418 Å) = 6.6 cm^{-1}. Space group $P2_1/c$ (C_{2h}) uniquely from the systematic absences: $0k0$ when $k \neq 2n$, $h0l$ when $l \neq 2n$. Sample dimensions: 0.18 × 0.20 × 0.30 mm.

Crystallographic Measurements. Oscillation and Weisenberg photographs yielded preliminary unit-cell parameters and space group information. Intensity data ($+h,+k,+l$) were recorded on an Enraf-Nonius CAD-4 diffractometer (Cu Kα radiation, incident beam graphite monochrometer; ω–2θ scans, θ_{max} = 67°). From a total of 3156 nonequivalent reflections recorded, those 2544 with $I > 3.0\sigma(I)$ were retained for the structure analysis, and the usual Lorentz and polarization corrections were applied. Refined unit-cell parameters were derived from the diffractometer setting angles for 25 reflections ($50° < \theta < 67°$) widely separated in reciprocal space.

Structure Analysis. The crystal structure was solved by direct methods.[36] Initial non-hydrogen atom coordinates were obtained from an *E*-map. Several rounds of full-matrix least-squares adjustment of positional and anisotropic thermal parameters for these 25 atoms were followed by evaluation of a difference Fourier synthesis, which yielded approximate coordinates for all hydrogen atoms. Inclusion of hydrogen atom positional and isotropic thermal parameters as variables in the subsequent least-squares cycles led to convergence at R = 0.035 (R_w = 0.052).[38] Final atomic parameters are included in the supplementary material.[37] Neutral atom scattering factors used in the structure-factor calculations were taken from ref 50. In the least-squares iterations, $\sum w\Delta^2|$ [$w = 1/\sigma^2(|F_0|)$, $\Delta = (F_0| - |F_c|)$] was minimized.

Biology. Inhibition of SRS-A Release from Lung (in Vitro). Sensitization of Animals. The release of SRS-A was studied in lungs from actively sensitized guinea pigs. Male Hartley guinea pigs (250–300 g, obtained from Charles River) were sensitized with 5 mg of ovalbumin injected intraperitoneally and 5 mg subcutaneously in 1 mL of saline on day 1 and 5 mg of ovalbumin injected intraperitoneally on day 4. The sensitized animals were used 3–4 weeks later.

Release of SRS-A. Sensitized guinea pigs were killed by a blow to the head, and the lungs were removed and cleaned of visible connective tissue, trachea, and large blood vessels. The lungs from individual animals were sliced into fragments approximately 1 mm in thickness by using a McIlwain chopper and then washed with oxygenated Tyrode's buffer. Weighed aliquots (approximately 400 mg wet weight) of lung were transferred into vials containing 2 mL of fresh Tyrode's solution with 10 mM cysteine and incubated in the presence or absence of test compound for 12 min at 37 °C followed by challenge of the tissue with 20 μg of ovalbumin/mL (final concentration). After an additional 0.25-h incubation, the vials were cooled to 4 °C and 1.5 mL of clear supernatant media was removed and mixed with 6 mL of cold 100% ethanol. This mixture was thoroughly vortexed and kept at −15 °C for 0.5 h to allow precipitation of protein. The samples were then centrifuged at 1000*g* for 0.25 h at 2 °C, and the clear supernatant fluid was removed in polyethylene tubes and taken to dryness at 50 °C under a stream of nitrogen gas. The samples were stored at −70 °C until assayed for SRS-A.

Bioassay of SRS-A on Guinea Pig Ileum. Male guinea pigs were killed by a blow to the head. A section of terminal ileum was removed, the lumen was cleaned, and the tissue was divided into four segments of 2.5 cm each. Each segment was suspended in a 5-mL organ both containing Tyrode's solution with 1 × 10^{-6} M mepyramine. The Tyrode's solution was constantly gassed with 95% oxygen/5% carbon dioxide and maintained at 32 °C with a constant temperature circulating unit. A counterweight of 0.5 g was applied to each tissue, and isotonic contractions were measured with a Harvard Apparatus smooth muscle transducer and recorded on a Harvard Apparatus biograph.

The lung samples to be assayed were dissolved in distilled water and added to the ileum in amounts sufficient to induce a measureable contraction. The amount of SRS-A in the sample was quantified by comparison against a dose–response produced to an in-house standard of SRS-A generated by antigen challenge in the peritoneum of sensitized rats.[51]

One unit of SRS-A was arbitrarily defined as the amount producing the same contractile response on the ileum as 1 nmol of histamine. The identity of SRS-A was established by (1) antagonism of bioactivity with FPL 55712, (2) loss of activity on incubation with soybean lipoxygenase, and (3) detection by HPLC. The data was calculated as percent inhibition of SRS-A in samples treated with test compound compared to similar samples treated with vehicle placebo. The data are presented as the mean percent inhibition from three to four lungs per treatment. In almost all cases for compounds producing greater than 40% inhibition the standard error of the mean (SEM) was less than 15% of the mean.

SRS-A Mediated Allergic Bronchospasm in Guinea Pigs. Allergic bronchospasm was measured in actively sensitized guinea pigs by a modification of the procedure of Konzett and Rossler.[52] Male Hartley guinea pigs were sensitized as described above. The sensitized animals were used 3–4 weeks later. To measure anaphylactic bronchospasm, sensitized guinea pigs were fasted overnight and the following morning anesthetized with 0.9 mL/kg intraperitoneally dialurethane, 0.1 g/mL diallylbarbituric acid, 0.4 g/mL ethylurea, and 0.4 g/mL urethane. The trachea and jugular vein were cannulated, and the animals were ventilated by a Harvard rodent aspirator at 50 strokes/min with a stroke volume of 5 mL. A side arm to the tracheal cannula was connected to a Harvard pressure transducer to obtain a continuous measure of inflation pressue, which was recorded on a Harvard polygraph. An increase in inflation pressure was taken as a measure of bronchoconstriction.

Each guinea pig was injected intravenously with 1 mg/kg propranolol, 5 mg/kg indomethacin and 2 mg/kg mepyramine together in a volume of 1 mL/kg. Fifteen minutes later, the animals were challenged with antigen (0.5% ovalbumin) delivered as an aerosol generated from a DeVilbiss Model 65 ultrasonic nebulizer and delivered through the tracheal cannula for 0.5 min. Bronchoconstriction was measured as the peak increase in inflation pressure that occurred during 15 min after antigen challenge. The effect of compounds on anaphylactic bronchospasm is expressed as percent inhibition of the peak increase in inflation pressure

(50) *International Tables for X-Ray Crystallography*; Kynoch: Birmingham, England, 1974; Vol. IV.

(51) Koopman, W. J.; Orange, R. P.; Austen, K. F. *Proc. Soc. Exp. Biol. Med.* **1971**, *137*, 64.

(52) Konzett, H.; Rossler, R. *Arch. Exp. Pathol. Pharmacol.* **1940**, *195*, 71.

compared to the peak increase in a control group receiving vehicle alone. The test compounds were administered by gavage (2 mL/kg) as a suspension in 0.4% methylcellulose in isotonic saline. The data are presented as the mean percent inhibition from four to five animals per treatment. In almost all the cases for compounds producing greater than 40% inhibition, the standard error of the mean (SEM) was less than 15% of the mean.

Inhibition of Antigen-Stimulated LTD_4 Production in Guinea Pig Lung. HPLC Measurement of Antigen Stimulated LTD_4 Production in Guinea Pig Lung. Sensitized lung fragments (4.8 g) obtained from four animals were incubated in aliquots of 0.4 g with antigen as described above. The incubations were terminated by the addition of four volumes of ethanol. The ethanol extracts were combined, and the ethanol was removed under reduced pressure at 50 °C. The residue was dissolved in 3.5 mL water, and the leukotrienes were extracted with acidic 2-propanol/ether and further partitioned between chloroform and aqueous methanol using the procedure described by Clancy and Hugli.[53] This material was subjected to HPLC analysis with a Waters M-6000 pump and a Du Pont Zorbox ODS 5μ 5 × 250 mmL column developed with the solvent mixture methanol/water/acetic acid, 07/33/0.08, adjusted to pH 6 with ammonium hydroxide and also containing 1 mM ethylenediaminetetraacetic acid (EDTA). The flow rate was 1 mL/min, and the effluent was monitored at 280 nm with a Waters Model 480 variable-wavelength detector. The elution time in minutes of reference standards was LTC_4 = 13.9 ± 0.5, LTD_4 = 24.2 ± 0.8, LTB_4 = 26.5 ± 0.9, and PGD_1 = 16.6 ± 0.5. The identity of the principal (>90%) peptidoleuktriene component released by antigen-challenged guinea pig lung in this experiment was LTD_4. Identification was based upon coelution with an authentic standard of the UV (280 nm) absorbing material, bioactivity (SRS-A), Table V, and radioimmunoassay to LTC_4/LTD_4 antiserum. LTD_4 was quantitated on the basis of a standard curve for injected LTC_4 (10–200 pmol). The overall recovery of [^{3}H]LTD_4 in this extraction procedure was 40%. The amount of LTD_4 formed in antigen-challenged lung tissue was 82 pmol/g. There was no detectable LTD_4 from unsensitized guinea pig lung by using either the UV or the bioassay procedure.

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Registry No. **1a**, 2942-59-8; **1b**, 40134-18-7; **1c**, 1452-94-4; **1d**, 5345-47-1; **1e**, 13362-26-0; **1f**, 30529-70-5; **1g**, 29241-65-4; **1h**, 114381-79-2; **1i**, 99058-34-1; **2aa**, 95-55-6; **3a**, 114501-02-9; **3b**, 57978-47-9; **3c**, 4394-09-6; **3d**, 115891-03-7; **3e**, 115891-04-8; **3f**, 115891-05-9; **3g**, 115891-06-0; **3h**, 75910-24-6; **3i**, 115891-07-1; **3j**, 115891-08-2; **3k**, 17782-05-7; **3l**, 4394-04-1; **3m**, 55285-35-3; **3n**, 115891-09-3; **3o**, 57978-51-5; **3p**, 115891-10-6; **3q**, 57978-41-3; **3r**, 115891-11-7; **3s**, 115891-12-8; **3t**, 68671-71-6; **3u**, 33522-80-4; **3v**, 115891-13-9; **3w**, 115891-14-0; **3x**, 54530-68-6; **3y**, 115891-15-1; **3z**, 115891-16-2; **3aa**, 115891-17-3; **3bb**, 51269-84-2; **3cc**, 115891-18-4; **3dd**, 115891-19-5; **3ee**, 59361-45-4; **3ff**, 17737-66-5; **3gg**, 114501-07-4; **3hh**, 114501-09-6; **3ii**, 51947-86-5; **3jj**, 115891-20-8; **3kk**, 115891-21-9; **3ll**, 115891-22-0; **3mm**, 115891-23-1; **3nn**, 115891-24-2; **3oo**, 95473-99-7; **3pp**, 115891-25-3; **3qq**, 114501-03-0; **3rr**, 115891-26-4; **3ss**, 115891-27-5; **3tt**, 115891-28-6; **3uu**, 115891-29-7; **3vv**, 115891-30-0; **3ww**, 51703-20-9; **3xx**, 115891-31-1; **3yy**, 115891-32-2; **3zz**, 115891-33-3; **3aaa**, 115891-34-4; **3bbb**, 115891-35-5; **3ccc**, 115891-36-6; **3ddd**, 115891-37-7; **3eee**, 115891-38-8; **3fff**, 115891-39-9; **3ggg**, 115891-40-2; **3hhh**, 115891-41-3; **3iii**, 115891-42-4; **4a**, 115891-43-5; **4b**, 115891-44-6; **4c**, 115891-45-7; **4d**, 115891-46-8; **4e**, 115891-47-9; **4f**, 115891-48-0; **4g**, 115891-49-1; **4h**, 115891-50-4; **4i**, 115891-51-5; **4j**, 115891-52-6; **4k**, 115891-53-7; **4l**, 115891-54-8; **4m**, 115891-55-9; **5**, 115891-56-0; **6**, 22961-45-1; **7**, 115891-57-1; **8**, 35708-19-1; **9**, 89109-19-3; **10**, 16100-58-6; **11**, 89109-20-6; **11**·Na, 89109-21-7; **12**, 89108-58-7; **13**, 115891-59-3; **14**, 115891-60-6; **15**, 115891-61-7; **15**·HCl, 115891-62-8; **16**, 115891-63-9; **17**, 115891-64-0; **18**, 97355-56-1; **19**, 89108-61-2; **20**, 115891-65-1; **21**, 115891-66-2; **22**, 115891-67-3; **23**, 115891-68-4; **24**, 115891-69-5; **25**, 115891-70-8; **26**, 115891-71-9; **27**, 115891-72-0; **28**, 115891-73-1; **29**, 115891-74-2; **30**, 115891-75-3; **31**, 115891-76-4; **32**, 115891-77-5; **33**, 115891-78-6; **34**, 115891-79-7; **35**, 115891-80-0; **36**, 115891-81-1; **37**, 115891-82-2; **38**, 115891-83-3; **39**, 115891-84-4; **40**, 115891-85-5; **41**, 115891-86-6; **42**, 115891-87-7; **43**, 115912-58-8; **44**, 115891-88-8; **45**, 89109-04-6; **46**, 115891-89-9; **47**, 115891-90-2; **48**, 89108-93-0; **49**, 89109-06-8; **50**, 89109-07-9; **51**, 115891-91-3; **52**, 89108-89-4; **53**, 89108-96-3; **54**, 89109-00-2; **55**, 115891-92-4; **56**, 115891-93-5; **57**, 115891-94-6; **58**, 115891-95-7; **59**, 115891-96-8; **60**, 115891-97-9; **61**, 115891-98-0; **62**, 110892-67-6; **63**, 115891-99-1; **64**, 89109-01-3; **65**, 89109-03-5; **66**, 89109-05-7; **67**, 115892-00-7; **68**, 89109-28-4; **69**, 115892-01-8; **70**, 115892-02-9; **71**, 115892-03-0; **72**, 115892-04-1; **73**, 115892-05-2; **74**, 115892-06-3; **75**, 115892-07-4; **76**, 89109-18-2; **77**, 115892-08-5; **78**, 115892-09-6; **79**, 115892-10-9; **80**, 115892-11-0; **81**, 115892-12-1; **82**, 115892-13-2; **83**, 115892-14-3; **84**, 115892-15-4; **85**, 115892-16-5; **86**, 115892-17-6; **87**, 115892-18-7; **88**, 89109-14-8; **89**, 115892-19-8; **90**, 95474-02-5; **91**, 89108-73-6; **92**, 115892-20-1; **93**, 89109-17-1; **94**, 115892-21-2; **95**, 115892-22-3; **96**, 115892-23-4; **97**, 115892-24-5; **98**, 89108-59-8; **99**, 89108-75-8; **100**, 115892-25-6; **101**, 89108-84-9; **102**, 115892-26-7; **103**, 115892-27-8; **104**, 89108-62-3; **105**, 95474-00-3; **106**, 89108-76-9; **107**, 115892-28-9; **108**, 89108-63-4; **109**, 89108-78-1; **110**, 115941-36-1; **111**, 89108-86-1; **112**, 110892-69-8; **113**, 115892-29-0; **114**, 89108-71-4; **115**, 89108-54-3; **116**, 89108-72-5; **117**, 115892-30-3; **118**, 115892-31-4; **119**, 89108-70-3; **120**, 89108-65-6; **121**, 115892-32-5; 2-$CH_3OC_6H_4NH_2$, 90-04-0; 3-$CH_3OC_6H_4NH_2$, 536-90-3; 4-$CH_3OC_6H_4NH_2$, 104-94-9; 3,4,5-$(CH_3O)_3C_6H_2NH_2$, 24313-88-0; 4-*n*-$C_4H_9OC_6H_4NH_2$, 4344-55-2; 4-$PhOC_6H_4NH_2$, 139-59-3; 4-$PhCH_2OC_6H_4NH_2$, 6373-46-2; 2-$CH_3SC_6H_4NH_2$, 2987-53-3; 3-$CH_3SC_6H_4NH_2$, 1783-81-9; 4-$CH_3SC_6H_4NH_2$, 104-96-1; 2-$CH_3C_6H_4NH_2$, 95-53-4; 2,6-$(CH_3)_2C_6H_3NH_2$, 87-62-7; 4-*n*-$C_4H_9C_6H_4NH_2$, 104-13-2; 3,4-$(CH_2)_3C_6H_3NH_2$, 24425-40-9; 4-$FC_6H_4NH_2$, 371-40-4; 2,4-$(F)_2C_6H_3NH_2$, 367-25-9; 3-$ClC_6H_4NH_2$, 108-42-9; 4-$CH_3COC_6H_4NH_2$, 99-92-3; 3-CO_2H, 4-$OHC_6H_3NH_2$, 89-57-6; 3-$PyNH_2$, 462-08-8; $PhCH_2NH_2$, 100-46-9; *n*-$C_6H_{13}NH_2$, 111-26-2; $(CH_3)_2N(CH_2)_2NH_2$, 108-00-9; $PhNH_2$, 62-53-3; 3,4-$(CH_3O)_2C_6H_3NH_2$, 6315-89-5; 3-$CF_3C_6H_4NH_2$, 98-16-8; 2-CH_3,3-$ClC_6H_3NH_2$, 87-60-5; $PrCO_2Et$, 105-54-4; $C_6H_{11}(CH_2)_2CO_2Et$, 10094-36-7; $PhCH_2CO_2Et$, 101-97-3; $Ph(CH_2)_5CO_2Et$, 52692-51-0; $Me_2C{=}CH(CH_2)_2CO_2Et$, 42272-93-5; $EtO(CH_2)_2Br$, 592-55-2; $(CH_3)_2CO_2(CH_2CH)CH_2Br$, 36236-76-7; $HOCH_2CH(OH)CH_2Br$, 4704-77-2; $HO(CH_2)_2Br$, 540-51-2; $HO(CH_2)_3Br$, 627-18-9; $(CH_3)_2N(CH_2)_2Br$·HCl, 106536-45-2; $(CH_3)_2N(CH_2)_3Br$·HCl, 72900-22-2; cyanomethyl 2-(*o*-methoxyanilino)nicotinate, 115892-33-6; ethyl caproate, 123-66-0; allyl bromide, 106-95-6; bis(2,4,6-trichlorophenyl) 2-*n*-butylmalonate, 77510-25-9; diethyl (3-methyl-2-butenyl)malonate, 22539-80-6; ethyl 5-methylhex-4-enoate, 42272-93-5; methyl 2-[4-[1,1-(ethylenedioxy)ethyl]-anilino]nicotinate, 115892-34-7; 1-[4-[1,1-(ethylenedioxy)ethyl]-phenyl]-3-*n*-butyl-4-hydroxy-1,8-naphthyridin-2(1*H*)-one, 115892-35-8; (*o*-hydroxyanilino)nicotinic acid, 4394-08-5; hexanoic anhydride, 2051-49-2; ethyl levulinate, 539-88-8; ethyl 5,5-(ethylenedioxy)levulinate, 115892-36-9; ethyl 4-(2-pyridyl)butyrate, 84199-93-9; 1-phenyl-3-(2-pyridylethyl)-4-acetoxy-1,8-naphthyridin-2(1*H*)-one, 115892-37-0; 1-phenyl-3-(2-*N*-methylpyridinium)-4-acetoxy-1,8-naphthyridin-2(1*H*)-one methyl sulfate, 115892-39-2; propanoic anhydride, 123-62-6; heptanoic anhydride, 626-27-7; ethyl decanoate, 110-38-3; ethyl cyclohexylacetate, 5452-75-5; 2-pyridineacetic acid ethyl ester, 2739-98-2.

Supplementary Material Available: Tables of atomic positional and thermal parameters, interatomic distances and angles, torsion angles and displacements of atoms from selected least-squares planes for **115** (7 pages). Ordering information is given on any current masthead page.

(53) Clancy, R. M.; Hugli, T. E. *Anal. Biochem.* **1983**, *133*, 30.