6. *Tilcotil*® Studies

Part 2

[4 + 2] Additions with Isothiazol-3(2*H*)-one 1,1-Dioxide

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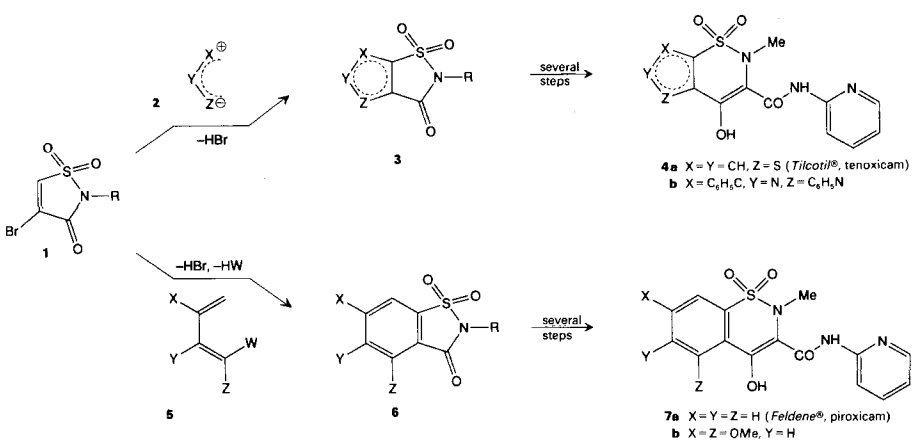
(28.XI.89)

The isothiazole **1** is not only a dipolarophile but also a reactive and versatile dienophile: especially with oxy-substituted 'donor' 1,3-butadienes, it readily combines in *Diels-Alder* fashion; the regiospecificity of the addition is governed by the carbonyl group of the dienophile, whereas the sulfo group can be ignored for the purpose of predicting regioselectivity. Upon dehydrobromination of the [4 + 2] adducts with DBN, the cycloaromatization process is completed, generating saccharin-like compounds. Besides the parent substance saccharin (**14b**), several hydroxylated derivatives have been synthesized by this new method; two of them, *i.e.* **16b** and **18c**, are of potential interest as non-nutritive sweetening agents *(Scheme 3)*. In an alternative version of this principle, the isothiazole **22** is reacted with the renowned oxazole **21**, affording, after acid-promoted rearrangement, pyrido-annelated isothiazoles **25** *(Scheme 4)*. Since both processes generate saccharin-related structures, they may serve in syntheses of oxicams and analogs of ipsapirone. To demonstrate the viability of the approach, one representative of each series, *i.e.* **26a** and **29**, has been converted to an oxicam (**7b** and **31c**, resp.; *Scheme 5*).

1. Introduction. – The oxicams, exemplified in *Scheme 1* by the structures **4a** (*Tilcotil*®, tenoxicam [1]) and **7a** (*Feldene*®, piroxicam [2]), are agents for an important improvement of existing antiinflammatory therapies [3]. Even though their mode of

Scheme 1



action (inhibition of prostaglandin synthesis) is similar to that of the major antecedent NSAID's, the oxicams excel with respect to potency and duration of action.

Retrosynthetically, the task of preparing oxicams can be reduced [4] to the theme of making (or taking!) the preceding annelated isothiazoles, *i.e.* heterocyclic (such as **3**) or carbocyclic (such as **6**) analogs of saccharin. At the time when tenoxicam (**4a**) was entering clinical trials, and piroxicam (**7a**) was already enjoying commercial success, we decided to face the problem of general synthetic access to saccharin derivatives. For the heterocyclic analogs **3** *(Scheme 1)*, a viable solution was found in a novel, regiospecific [3 + 2] cycloaddition of 1,3-dipolar agents **2** to the dipolarophilic synthon **1** [5], furnishing various heterocyclic species **3**, and eventually an illustrative oxicam **4b**. The question was, therefore, apparent: would the synthon **1** similarly act as the dienophile component of a *Diels-Alder* reaction with various dienes **5**, uncovering a new path to saccharin derivatives **6**?

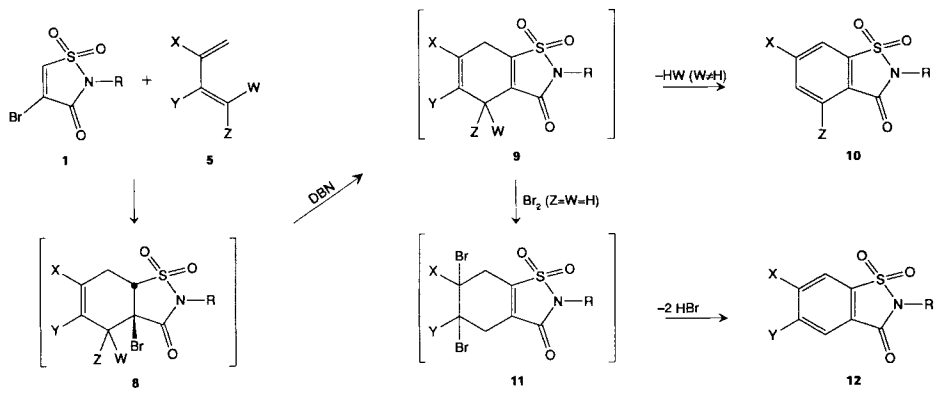
Apart from general considerations, there was good reason to expect that **1** would behave as a fairly reactive dienophile, since simpler dienes have previously undergone [4 + 2] additions with the closely related β-sulfoacrylic anhydride [6] and with isothiazol-3(2*H*)-one 1-monoxide [7]; most recently, the 1,1-dioxide derivatives themselves have served as dienophiles [8] in the synthesis of a number of compounds related to ipsapirone (a buspirone-type 5-HT receptor inhibitor). Still apparently missing is the crucial aromatization step of the initially formed *Diels-Alder* adducts with preservation of the sulfo group, an indispensable process if substituted analogs of saccharin, oxicams, or ipsapirone are to be generated. In the following, such a process and its application to oxicam synthesis is described.

2. Saccharin Derivatives *via Diels-Alder* Reaction. – 2.1. *General Considerations.* In view of the resurging interest in non-nutritive sweetening agents [9], it seems remarkable that few new synthetic methods have been added to the existing principles of saccharin synthesis [10] for at least 20 years, *i.e.* since the topic was last reviewed intensively [11]. The most recent – and perhaps the most notable – entry to the field consists in the *ortho*-carboxylation of benzenesulfonamides [12], cyclization to the sulfimide is achieved with polyphosphoric or sulfuric acid. The available procedures are neither generally applicable nor compatible with sensitive substituents.

Access to saccharins by *Diels-Alder* reaction would remedy part of this complication, especially since a number of oxy-substituted 'donor' 1,3-butadienes have become standard units of the *Diels-Alder* construction set (for a review, see [13]). In practice, we found this approach to be a valuable advancement of the existing methodology, providing access not only to novel oxicams **7** (as well as **31**, see below, *Scheme 5*), but also to saccharin (**14b**) itself and to the sweeteners **16b** [14] and **18c** [15] which, until now, have been difficult to synthesize.

The principle is outlined in *Scheme 2:* 1,3-butadienes of the general structure **5** are added in *Diels-Alder* fashion to the dienophilic component 4-bromoisothiazol-3(2*H*)-one 1,1-dioxide **1** [5], producing an adduct **8** where X, Y, Z, and W each represent either a H-atom or donor substituents such as AcO, MeO, or Me_3SiO groups. The ensuing dehydrobromination is then performed most effectively with the bicyclic amidine base DBN (= 1,5-diazabicyclo[4.3.0]non-3-ene). The resulting 4,7-dihydrosaccharin derivative **9** will then spontaneously aromatize to **10** if either Z or W (or both) are O-sub-

Scheme 2



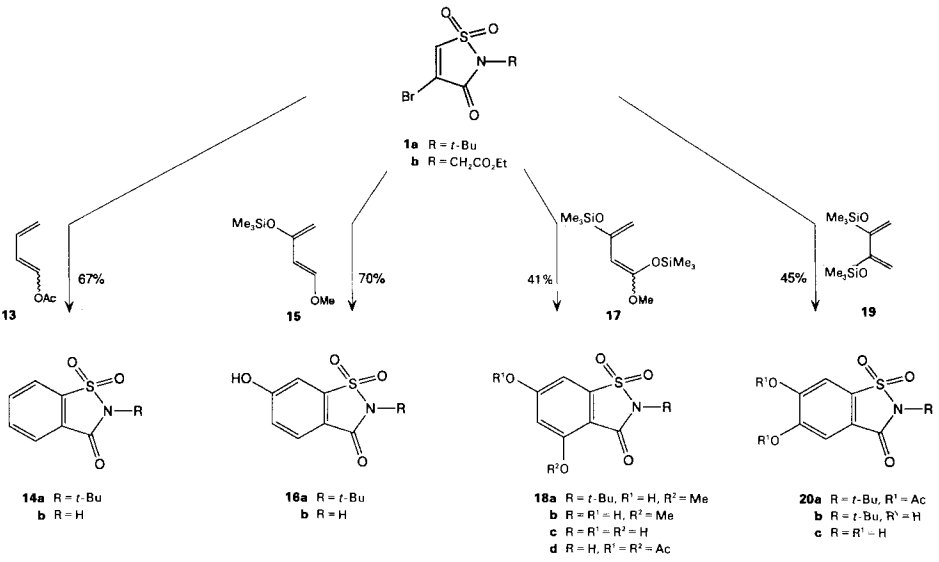
stituents; if, on the other hand, both W and Z are H-atoms, an extra dehydrogenation step is required in order to complete the cycloaromatization process. This is achieved by adding Br_2 to the electron-rich double bond. The tetrahydrosaccharin **11** thus formed loses two molecules of HBr *in situ,* affording a saccharin derivative with the alternative substitution pattern **12**. The approach has been used previously to synthesize 4,5-dihydroxyphthalates *via* the *Diels-Alder* reaction [16].

There remains the question of regioselectivity when unsymmetrically substituted butadienes are employed. The closely related case of the [4 + 2] addition of electron-rich dienes to quinones has been subjected to arguments of the frontier molecular orbital theory [17]; the predictions with respect to regioselectivity have been found to agree with those based on resonance theory as well as with experimental observations. If our previous experience with **1** as a dipolarophile [5] were to be any guide, the presence of the sulfo group could be ignored for the purpose of determining regiospecificity, while it would still improve the total acceptor reactivity. As detailed below for several individual butadienes, these expectations proved to be justified: with regard to *Diels-Alder* regioselectivity, the synthon **1** does indeed behave like an unsubstituted acrylate; as for reactivity, the superior acceptor qualities of *e.g.* maleic anhydride are preserved.

2.2. *Addition of 1,3-Butadienyl Acetate.* The diene **13**, which can be prepared easily from methacrolein and isopropenyl acetate [18], is now commercially available. Even though it does not rank among the most reactive oxy-substituted dienes, it reacts quite readily with the dienophile **1a** *(Scheme 3)*. The adduct undergoes smooth dehydrobromination upon treatment with DBN furnishing 2-(*tert*-butyl)saccharin (**14a**) in 67% yield, from which saccharin (**14b**) can be liberated quantitatively upon CF_3COOH treatment. No attempt has been made at scaling up or optimizing this sequence, since more practical means obviously exist for the preparation of the parent compound.

2.3. *Addition of* trans-*1-Methoxy-3-(trimethylsilyloxy)buta-1,3-diene* (**15**). The most familiar of all 'donor' butadienes, **15**, can be rated among the most versatile and reactive synthons (commercially available). Regiospecific *Diels-Alder* reactions are its most frequent application [19], and it has been used for annelation reactions with acrylates, methylidenelactones, and benzoquinone [20]. It must be noted, though, that whenever an oxidized S-atom was present in the acceptor part [21], such as in the key step of the

Scheme 3



prephenate total synthesis [22], the S-atom always functioned as a leaving group, whereas in the envisioned processes of *Scheme 3*, the sulfo group evidently has to be preserved. In practice, even though elimination of SO_2 (leading to hydroxylated benzamides) proved to be a complication, reaction conditions could be established for all present cases which would assure the preservation of the sulfo moiety.

The dienophile **1a** reacts with **15** in refluxing benzene, affording, after elimination of HBr with DBN, the 6-hydroxysaccharin derivative **16a** in 70% yield *(Scheme 3)*. Free 6-hydroxysaccharin (**16b**) is released in 92% yield when **16a** is refluxed with CF_3COOH. The purity of **16b** (see *Exper. Part*) as well as its extremely sweet taste [15] (the 5-OH isomer is apparently not sweet [23]) leave no doubt with respect to the regioorientation of the *Diels-Alder* addition. Moreover, this straightforward path to 6-hydroxylated saccharin might compare favorably with the classical procedure [14].

2.4. *Addition of (*E/Z*)-1-Methoxy-1,3-bis(trimethylsilyloxy)buta-1,3-diene* (**17**). Diene **17** [24], resembling diene **15** in reactivity and selectivity, offers the option of rescuing two phenolic OH groups past the cycloaromatization step. The dienophile **1a** reacts at 100° with diene **17** *(Scheme 3)*; care must be taken to avoid the loss of SO_2 from the initial adduct. As in the case above, this can be properly assured by carrying out the DBN-induced HBr elimination at once, *i.e.* as soon as the adduct formation is complete. After workup, including a treatment with aqueous acid, **18a** is isolated in 41% yield (with the dienophile **1b**, this reaction was later optimized to afford a 52% overall yield of the corresponding **26a**; see *Chapt. 4*).

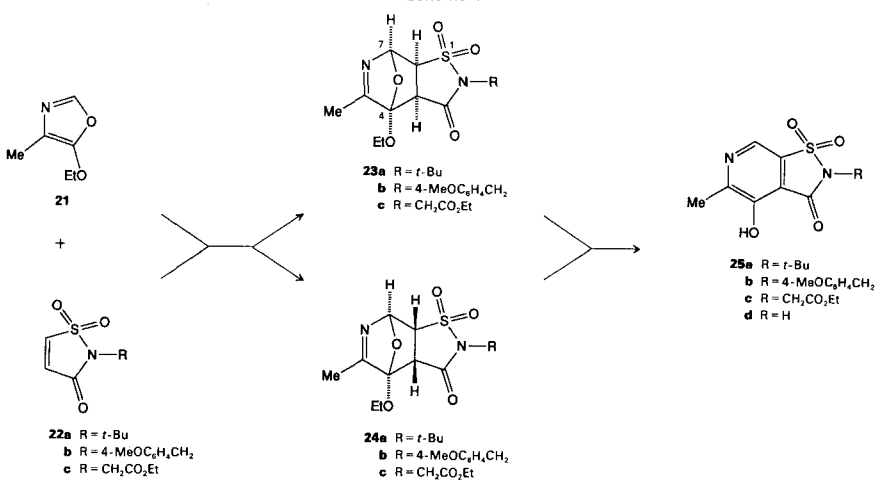
To complete the sequence, the *t*-Bu group is split off with hot CF_3COOH and the MeO group in **18b** cleaved smoothly with BBr_3, affording the other sweet compound of this series, **18c** (the sweet taste is lost, when the phenolic groups are acetylated, as in **18d**). If any uncertainty were still remaining with regard to the regiochemical reaction course, it

should be allayed by the fact that 4,6-dihydroxysaccharin (**18c**) thus prepared is sweet. A corresponding 5,7-dihydroxy derivative would in all probability not be sweet (for structure-taste relationship of various saccharin and acesulfam derivatives, see [23]).

2.5. *Addition of 2,3-Bis(trimethylsilyloxy)buta-1,3-diene* (**19**). Diene **19** [25], without doubt the least reactive of this series, still combines with many electron-deficient dienophiles in *Diels-Alder* fashion [16] [26]. It is preferably prepared by direct silylation of butane-2,3-dione [27]. With the dienophile **1a**, it reacts at 120° in the absence of any solvent. The crude adduct is then sequentially dehydrobrominated, dehydrogenated with Br_2, and acylated for facilitating chromatography, furnishing the 5,6-diacetoxysaccharin derivative **20a** in 45% overall yield *(Scheme 3)*. The dihydroxy derivative **20b** is liberated from it upon base-induced transesterification and the free saccharin **20c** finally obtained after treatment with CF_3COOH. None of these compounds taste sweet.

3. Sulfo Analogs of Pyridoxine *via Diels-Alder* Reaction. – The oxazole **21** *(Scheme 4)*, one of the cornerstones of pyridoxine (= vitamin B_6) synthesis [28], adds in [4 + 2] manner even to unreactive dienophiles [29]. In the case at hand, the problem of retaining the sulfo group during the ensuing cycloaromatization step is potentially acute, since a sulfone function has previously served as leaving group in a closely related process [30].

Scheme 4



The primary *Diels-Alder* adducts are usually – but not invariably [31] – too labile to be isolated and are, therefore, at once elaborated into pyridines, furans *etc.* Isothiazolo[5,4-*b*]-pyridines (= '4-aza-saccharins') have become accessible just recently [32] *via* a closely related cycloaddition of the corresponding dienes [33] to **22a**. The topic has been reviewed recently [34].

In fact, **21** combines with **22** at room temperature (!), forming surprisingly stable and isolatable *Diels-Alder* adducts **23** and **24**. The *'exo'*- and *'endo'*-components are easily identified by ^{1}H-NMR spectroscopy: in the *'exo'*-adducts **23**, H–C(7) forms a *s*, whereas in the *'endo'*-adducts **24**, H–C(7) is recorded as a *d* ($J(7,7a\beta) = 3.5$ Hz). Usually, the

'exo'-adducts prevail. Nevertheless, presence of a bulky *N*-substituent in **22** (such as the *t*-Bu group in **22a**) appears to direct the kinetics of the process partially towards *'endo'*-formation. Thus, **22a** reacts with **21** to yield a 5:3 *'exo/endo'*-mixture **23a/24a**. The individual components can be separated by fractional crystallization and are not subject to subsequent thermal equilibration, indicating that the reaction progresses with kinetic control.

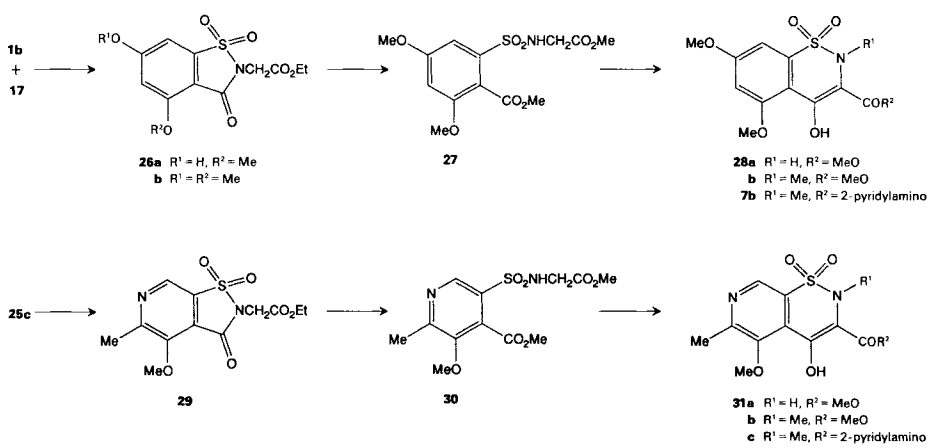
With respect to regiospecificity, it would seem justified to expect the reaction to follow the pattern observed previously with the dienes of *Scheme 3*. There is also precedence [35] for the fact that with unsymmetrical dienophiles, the most electronegative center ends up in position 3 of the adduct (and thus in position 4 of the rearranged pyridine derivative). This behavior can be rationalized in terms of frontier MO theory [35].

The rearrangement of the *'exo'*- as well as the *'endo'*-adducts occurs smoothly with acid catalysis, essentially under conditions established for pyridoxine synthesis [28]: the 'pyridosaccharins' **25** can be isolated in up to 81% yield. The free saccharin **25d** (again no sweetener) is obtained from the *N*-(4-methoxybenzyl) compound **25b** upon treatment with CF_3COOH in the presence of anisole. For an application to oxicam synthesis, the respective acetic-acid derivative **25c** can be prepared analogously.

4. Transformation into Oxicams. – The conversion of esters of saccharin-*N*-acetic acid to oxicams has been the key feature of the synthesis of piroxicam [4] and also of several closely related heterocyclic species [5]. Since we had been engaged in the above venture within the context of an antiinflammatory research project, we undertook to prove the value of these novel 'saccharins' in oxicam synthesis.

As summarized in *Scheme 5*, the dienophile **1b** is combined with diene **17**, producing **26a** in 52% yield (see also *Chapt. 2.4*). The methylated derivative **26b**, on exposure to NaOMe, undergoes ring opening concomitant with transesterification to the diester **27** (76%), which in turn is cyclized in *Dieckman* fashion to the 1,2-thiazine **28a** with NaOMe in THF (51%). Selective methylation to **28b** (90%) is followed by a thermally promoted aminolysis with 2-aminopyridine, yielding finally 69% of oxicam **7b** ('5,7-dimethoxypiroxicam').

Scheme 5



26a R^1 = H, R^2 = Me
b R^1 = R^2 = Me

27

28a R^1 = H, R^2 = MeO
b R^1 = Me, R^2 = MeO
7b R^1 = Me, R^2 = 2-pyridylamino

29

30

31a R^1 = H, R^2 = MeO
b R^1 = Me, R^2 = MeO
c R^1 = Me, R^2 = 2-pyridylamino

Similarly, in the pyrido-annelated series, the strongly acidic phenol **25c** is treated with diazomethane to give the methyl ether **29** (80%). The subsequent ring opening and transesterification have to be executed in separate steps: dimethyl ester **30** is thus obtained in 58% yield. *Dieckman* condensation proceeds in complete analogy to the case above, yielding 72% of the pyridothiazine **31a**, and as expected, a selective methylation then furnishes 71% of **31b**. Disappointing yields of **31c** (13%) cap this fairly involved sequence, when the sensitive ketoester **31b** is subjected to the harsh aminolysis conditions with 2-aminopyridine.

Neither **7b** nor **31c** equal the biological standards (piroxicam and tenoxicam) with respect to antiinflammatory potency.

5. Conclusion. – The isothiazoles **1** and **22** prove to be useful dienophiles. When subjected to the cycloaromatization described above, they give access to various hydroxylated saccharin analogs which, up to now, have been difficult to prepare. Some of these products may have the qualities required of a state of the art non-nutritive sweetening agent [15]; others may serve as intermediates if oxicams are the synthetic targets.

I would like to thank my colleagues of Central Research Units of *F. Hoffmann-La Roche AG* for the IR spectra (Dr. *M. Grosjean*, Mr. *A. Bubendorf*), NMR spectra (Dr. *W. Arnold*), MS (Dr. *W. Vetter* and Mr. *W. Meister*), and the elemental analyses (Dr. *A. Dirscherl*).

Experimental Part

(The author wishes to thank Mr. *Rolf Dittmar* and Mrs. *Heidy Schär-Morath* for their outstanding experimental contributions.)

General. M.p.: uncorrected. IR spectra (cm^{-1}): in KBr. ^{1}H-NMR spectra: chemical shifts in ppm rel. to TMS, coupling constants *J* in Hz. Correct elemental analyses were obtained for all compounds.

1. *2-(1,1-Dimethylethyl)-1,2-benzisothiazol-3(2*H*)-one 1,1-Dioxide* (**14a**). A soln. of 4-bromo-2-(*tert*-butyl)isothiazol-3(2*H*)-one 1,1-dioxide (**1a**; 0.53 g, 2 mmol) and buta-1,3-dienyl acetate (**13**; 0.67 g, 6 mmol) in dry toluene (4 ml) was maintained at reflux temp. for 20 h. The volatile components were removed under high vacuum, the oily residue was dissolved in CH_2Cl_2 (10 ml), and DBN (248 mg, 240 ml, 2 mmol) was injected. After 30 min at 20°, the soln. was partitioned between CH_2Cl_2 (30 ml) and 0.2N aq. HCl (30 ml), the org. phase dried (Na_2SO_4) and evaporated and the remaining oil chromatographed on 80 g of silica gel (CH_2Cl_2). Crystallization from CH_2Cl_2/hexane afforded colorless crystals of anal. pure **14a** (320 mg, 67%). M.p. 100–101°. IR: 1727*s*, 1600*w*. MS: 239 (M^+), 224 ([$M - CH_3$]$^+$), 184.

2. *2-(1,1-Dimethylethyl)-6-hydroxy-1,2-benzisothiazol-3(2*H*)-one 1,1-Dioxide* (**16a**). A soln. of **1a** (3.3 g, 12.3 mmol) and (*E*)-1-methoxy-3-(trimethylsilyloxy)buta-1,3-diene (**15**; 6.4 g, 37.2 mmol) in dry benzene (60 ml) was kept at reflux temp. for 2 h. The soln. was allowed to cool to 20° and DBN (1.53 g, 1.48 ml, 12.3 mmol) injected with stirring. After 30 min, the benzene was evaporated, the residual oil dissolved in THF (35 ml), aq. 2N HCl (60 ml) added, and the mixture stirred vigorously for another 30 min, it was then extracted with AcOEt, dried (Na_2SO_4), and evaporated. Recrystallization from CH_2Cl_2 afforded 1.35 g of white crystals of anal. pure **16a**. M.p. 204–205°. Chromatography of the mother liquor on silica gel (CH_2Cl_2/MeOH 99:1) gave further 0.85 g of **16a**. Total yield: 2.2 g (70%). Crystallization from AcOEt/hexane gave purest **16a**. M.p. 207–208°. IR: 3318*m*, 1724*m*, 1695*s*, 1614*m*, 1593*s*, 1498*s*. MS: 255 (M^+), 240 ([$M - CH_3$]$^+$), 200 ([$M - C_4H_7$]$^+$), 182.

3. *Ethyl 2,3-Dihydro-6-hydroxy-4-methoxy-3-oxo-1,2-benzisothiazol-3-acetate 1,1-Dioxide* (**26a**). A soln. of ethyl 4-bromo-2,3-dihydro-3-oxo-4-isothiazole-2-acetate 1,1-dioxide (**1b**; 10.0 g, 33.55 mmol) and (*E*/*Z*)-1-methoxy-1,3-bis(trimethylsilyloxy)buta-1,3-diene [24] (**17**; 17.5 g, 67.1 mmol) in dry toluene (120 ml) was stirred at 100° for 1.5 h under Ar. The soln. was cooled with an ice-bath, and under continuous stirring and cooling with ice, DBN (4.00 ml, 4.17 g, 33.55 mmol) was added dropwise. The ice-bath was removed, stirring continued for 15 min at r.t., the solvent evaporated, the residue dissolved in THF (100 ml), and 2N aq. HCl (100 ml) added. After 2 h of

stirring, the mixture was partitioned between H_2O (500 ml) and AcOEt (3 × 200 ml). The org. phases were dried (Na_2SO_4) and the volatile components removed under vacuum. The residue was dissolved again in hot AcOEt, treated with charcoal, and diluted with hexane to initiate crystallization. Off-white crystals of anal. pure **26a** (5.5 g, 52%) were collected. M.p. 237° (dec.). IR: 3380 (sh), 3300*m*, 1748*s*, 1704*s*, 1615/1578/1481*s*. ^{1}H-NMR (60 MHz, (D_6)DMSO): 1.20 (*t*, 3 H); 3.92 (*s*, 3 H); 4.17 (*q*, 2 H); 4.42 (*s*, 2 H); 6.84, 7.02 (*AB*, J = 1.8). MS: 315 (M^+), 242 ($[M - CO_2Et]^+$), 228, 150.

*2-(1,1-Dimethylethyl)-6-hydroxy-4-methoxy-1,2-benzisothiazol-3(2*H*)-one 1,1-Dioxide* (**18a**) was prepared similarly in 41% yield from **1a** and **17**. White solid from CH_2Cl_2. M.p. > 280°. IR: 3320*m*, 1694*s*, 1630/1585/1497*s*. MS: 285 (M^+), 270 ($[M - CH_3]^+$), 230 ($[M - C_4H_7]^+$).

4. *2-(1,1-Dimethylethyl)-2,3-dihydro-3-oxo-1,2-benzisothiazole-5,6-diyl Diacetate 1,1-Dioxide* (**20a**). A mixture of **1a** (10.0 g, 37.3 mmol) and 2,3-bis(trimethylsilyloxy)buta-1,3-diene [27] (**19**; 17.2 g, 74.6 mmol) was stirred vigorously for 5 h at 120° under Ar. The crude product was then transferred to a 1-l flask with dry CH_2Cl_2, and all volatile components were removed under high vacuum, leaving 25.5 g of crude product as an orange-red oil (consisting, presumably, of 18.6 g of *Diels-Alder* adduct **8** and 6.9 g of excess **19**). This mixture was dissolved in dry benzene (350 ml), and with stirring, DBN (4.63 g, 4.45 ml, 37.3 mmol) was injected within 5 min. Stirring at r.t. was continued for 45 min, as a white solid started precipitating from the red solution of **9**. While cooling with an ice-bath, a soln. of Br_2 (11.8 g, 3.8 ml, 73.9 mmol) in CCl_4 (300 ml) was added within 45 min. The solvents were evaporated, the dark residue was dried under high vacuum and the remaining 'tar' dissolved in dry pyridine (230 ml). Under Ar, Ac_2O (15.2 g, 14.1 ml, 149 mmol) was slowly added and the mixture stirred at 20° for 2.5 h. All volatile components were then evaporated under high vacuum, and the residue was partitioned between AcOEt (400 ml) and 0.1N aq. HCl (1000 ml). The aq. phase, containing insoluble components, was filtered, and the filtrate was reextracted with AcOEt. The org. phases were washed with sat. aq. $NaHCO_3$ soln. and evaporated. The residual dark oil (12 g) was chromatographed on 500 g of silica gel (AcOEt): 10.7 g of yellowish solid. After recrystallizing from AcOEt/hexane, white crystals of anal. pure **20a** (6.0 g 45% from **1a**) were obtained. M.p. 173–174°. IR: 1800*s*, 1729*s*, 1611/1480*m*. ^{1}H-NMR (80 MHz, (D_6)DMSO): 1.56 (*s*, 9 H); 2.39 (*s*, 3 H); 8.13 (*s*, 1 H); 8.41 (*s*, 1 H). MS: 340 ($[M - CH_3]^+$), 300 ($[M - C_4H_7]^+$), 298 ($[340 - C_2H_2O_2]^+$), 258, 256, 216, 215.

5. *2-(1,1-Dimethylethyl)-5,6-dihydroxy-1,2-benzisothiazol-3(2*H*)-one 1,1-Dioxide* (**20b**). To a soln. of **20a** (4.56 g, 12.8 mmol) in dry MeOH (150 ml) was added anh., finely powdered Na_2CO_3 (4.56 g, 43.0 mmol) and the suspension stirred vigorously for 1 h. The mixture was then poured into H_2O (500 ml) and acidified with 1N aq. HCl. The aq. soln. was extracted with AcOEt (3 × 100 ml) and the org. phase dried (Na_2SO_4) and evaporated. Anal. pure **20b** (3.41 g, 98%) was thus obtained as a white powder. Recrystallization from CH_2Cl_2/hexane gave white crystals. M.p. > 250°. IR: 3484/3440/3326*w*, 1742*s*, 1681*m* (possibly an artifact), 1603/1519*m*. ^{1}H-NMR (80 MHz, (D_6)DMSO): 1.66 (*s*, 9 H); 7.30 (*s*, 1 H); 7.33 (*s*, 1 H). MS: 271 (M^+), 256 ($[M - CH_3]^+$), 216 ($[M - C_4H_7]^+$), 198, 152.

6. *2-(1,1-Dimethylethyl)-4*α*-ethoxy-3a*α*,4,7*α*,7a*α*-tetrahydro-5-methyl-4,7-epoxyisothiazolo[5,4-c]pyridin-3(2H)-one 1,1-Dioxide* (**23a**; *'exo'*-Adduct) *and 2-(1,1-Dimethylethyl)-4*α*-ethoxy-3a*β*,4,7*α*,7a*β*-tetrahydro-5-methyl-4,7-epoxyisothiazolo[5,4-c]pyridin-3(2*H*)-one 1,1-Dioxide* (**24a**; *'endo'*-Adduct). A soln. of 2-(*tert*-butyl)-isothiazol-3(2*H*)-one 1,1-dioxide [5] (**22a**; 10.0 g, 52.8 mmol) and 5-ethoxy-4-methyloxazole [28] (**21**; 8.7 g, 68.7 mmol) in dry benzene (100 ml) was slowly evaporated and kept at r.t. for 1 h, after which time no more **22a** was detectable by TLC. Fractional crystallization from CH_2Cl_2/hexane afforded initially 2 fractions of **24a**, white crystals of m.p. 137–138° (totalling 5.34 g, 32%; contaminated with some **23a**), then subsequently 2 fractions of **23a**, white crystals of m.p. 115–116° (totalling 8.85 g, 53%; contaminated with some **24a**). Combined yield of the *Diels-Alder* reaction: 85%. After 1 further crystallization from CH_2Cl_2/hexane, isomer-free **24a** was obtained. M.p. 146–147°. IR: 1710*s*, 1633*m*, 1334/1155*s*. ^{1}H-NMR (80 MHz in $CDCl_3$): 1.38 (*t*, *X* of ABX_3, J_{BX} = 7.2, 3 H); 1.58 (*s*, 9 H); 2.19 (*s*, 3 H); 3.74 (*d*, *X* of *AMX*, J_{MX} = 9.5, 1 H); 3.70–4.25 (*m*, *AB* of ABX_3, J_{AB} = 9.5, $J_{AX} = J_{BX}$ = 7.2, 2 H); 4.32 (*dd*, *M* of *AMX*, J_{AM} = 3.5, J_{MX} = 9.5, 1 H); 6.05 (*d*, *A* of *AMX*, J_{AM} = 3.5, 1 H). MS: 301 ($[M - CH_3]^+$), 261 ($[M - C_4H_7]^+$), 187 ($[M - \mathbf{21}]^+$), 174 ($[M - (t\text{-Bu})NCO - MeCN]^+$).

Nearly isomer-free **23a** (major) was obtained after another recrystallization from CH_2Cl_2/hexane. M.p. 116°. IR: 1725*s*, 1635*m*, 1333/1147*s*. ^{1}H-NMR (80 MHz, $CDCl_3$): 1.33 (*t*, *X* of ABX_3, J_{BX} = 7.2, 3 H); 1.65 (*s*, 9 H); 2.21 (*s*, 3 H); 3.00 (*d*, J = 7.6, 1 H); 3.76 (*d*, J = 7.6, 1 H); 3.68–4.21 (*m*, *AB* of ABX_3, J_{AB} = 9.5, $J_{AX} = J_{BX}$ = 7.2, 2 H); 6.23 (*s*, 1 H). MS: identical with MS of **24a**.

Similarly prepared were the following *'exo'*-adducts (the minor *'endo'*-components were not isolated):

*4*α*-Ethoxy-3a*α*,4,7*α*,7a*α*-tetrahydro-2-(4-methoxybenzyl)-5-methyl-4,7-epoxyisothiazolo[5,4-c]pyridin-3(2*H*)-one 1,1-Dioxide* (**23b**). From **21** and **22b** in 45% yield. White crystals from AcOEt/hexane. M.p. 138–139°.

Ethyl 4α-Ethoxy-2,3,3aα,4,7α,7aα-hexahydro-5-methyl-3-oxo-4,7-epoxyisothiazolo[5,4-c]pyridine-2-acetate 1,1-Dioxide (**23c**). In 55% yield from **21** and **22c**. White crystals from benzene. M.p. 137–138°.

7. *Ethyl 2,3-Dihydro-4-hydroxy-5-methyl-3-oxoisothiazolo[5,4-c]pyridine-2-acetate 1,1-Dioxide Hydrochloride* (**25c**·HCl). Under Ar, **23c** (17.1 g, 49.4 mmol) was suspended in 340 ml of abs. EtOH (freshly distilled from Na). While stirring vigorously, a stream of dried (conc. H_2SO_4) HCl gas was bubbled through the suspension for 45 min (after 10 min, the suspension had completely dissolved, and product started precipitating after 30 min). At all times, the internal temp. was prevented from rising above 45° (water bath). The suspension was then cooled to −20° and stirred for another 30 min and the anal. pure **25c**·HCl collected as white crystals (13.4 g, 81%). M.p. 156–168° (↑ HCl). IR: 3440*m*, 3108*w*, 2470*m*, 1761*s*, 1749*s*, 1640*m*, 1558*s*, 1366/1196*s*. ^{1}H-NMR (80 MHz, (D_6)DMSO): 1.22 (*t*, 3 H); 2.59 (*s*, 3 H); 4.19 (*q*, 2 H); 4.57 (*s*, 2 H); 8.84 (*s*, 1 H); 9.75 (*s*, 2 H). MS: 300 (M^+), 227 ([$M - CO_2Et$]$^+$), 163 ([227 − SO_2]$^+$), 135, 108.

The free base **25c** was liberated by dissolving **25c**·HCl in aq. buffer soln. of pH 2 and extracting the product with CH_2Cl_2: white crystals from H_2O. M.p. 98–100°. IR, NMR, and MS: identical with those of **25c**·HCl.

Similarly prepared were:

4-Hydroxy-2-(4-methoxybenzyl)-5-methylisothiazolo[5,4-c]pyridin-3(2H)-one 1,1-Dioxide Hydrochloride (**25b**·HCl). In 80% yield from **23**. Yellowish powder. M.p. 148° (dec.).

2-(1,1-Dimethylethyl)-4-hydroxy-5-methylisothiazolo[5,4-c]pyridin-3(2H)-one 1,1-Dioxide Hydrochloride (**25a**·HCl). In 63% yield from **23a**. White powder. M.p. 182° (dec.).

8. *6-Hydroxy-1,2-benzisothiazol-3(2H)-one 1,1-Dioxide* (= *6-Hydroxysaccharin;* **16b**). Under Ar, a soln. of **16a** (6.8 g, 26.7 mmol) in freshly distilled CF_3COOH (130 ml) was stirred at reflux temp. for 24 h. The acid was evaporated and the residue repeatedly dissolved in AcOEt and evaporated again. The remaining solid was then dissolved in hot AcOEt and treated with charcoal until a colorless soln. resulted. Hexane was added to start crystallization: white crystals of anal. pure **16b** (4.9 g, 92%). M.p. 269–271° ([I4]: 264°). IR: 3274*s*, 1709*s*, 1578/1482*s*. MS: 199 (M^+), 135 ([$M - SO_2$]$^+$), 120, 92.

Similarly prepared were:

6-Hydroxy-4-methoxy-1,2-benzisothiazol-3(2H)-one 1,1-Dioxide (**18b**). Nearly quantitative yield from **18a**. White crystals. M.p. 335° (dec.). IR: 3200*s*, 1712*s*, 1604*s*, 1515/1498*w*. ^{1}H-NMR (80 MHz, (D_6)DMSO): 3.93 (*s*, 3 H); 6.86 (*d*, J = 1.7, 1 H); 6.95 (*d*, J = 1.7, 1 H); 10.9–11.9 (br., 2 H). MS: 229 (M^+), 165, 135, 121.

1,2-Benzisothiazol-3(2H)-one 1,1-Dioxide (= *Saccharin;* **14b**). Quantitative yield from **14a**. White crystals from acetone/hexane. M.p. 223–225°.

5,6-Dihydroxy-1,2-benzisothiazol-3(2H)-one 1,1-Dioxide (**20c**). In 70% yield from **20b**. Off-white crystals from AcOEt/hexane. M.p. > 250°. IR: 3502/3316/3244*m*, 1732*s*, 1600/1514*s*. ^{1}H-NMR (80 MHz, (D_6)DMSO): 7.26 (*s*, 1 H); 7.32 (*s*, 1 H); 10.4–11.2 (br. 2 H). MS: 215 (M^+), 151 ([$M - SO_2$]$^+$), 135, 123, 108.

9. *4-Hydroxy-5-methylisothiazolo[5,4-c]pyridin-3(2H)-one 1,1-Dioxide* (**25d**). The red soln. of **25b** (6.6 g, 17.9 mmol and anisole (11.7 g, 11.8 ml, 107.2 mmol) in CF_3COOH (200 ml) was kept at 50° for 17 h. The acid was evaporated and the residue partitioned between 4% aq. $NaHCO_3$ soln. (1300 ml) and Et_2O (500 ml) in order to remove the anisole. The aq. phase was cautiously brought to pH 2 with conc. aq. HCl soln. and extracted with AcOEt (2 × 500 ml and 2 × 200 ml), yielding I.7 g of brownish product. Continous extraction of the aq. phase with AcOEt overnight gave further 0.5 g of similar product. The combined AcOEt extracts were triturated with acetone, leaving a tan powder of anal. pure **25d** (1.3 g, 34%) as the insoluble part. M.p. > 250°. IR 3314/3090*m*, 1731*m*, 1621*s*. ^{1}H-NMR (80 MHz, (D_6)DMSO): 2.53 (*s*, 3 H); 8.66 (*s*, 1 H); 8.47–9.09 (br. 2 H). MS: 214 (M^+), 149 ([$M - SO_2$]$^+$).

10. *4,6-Dihydroxy-1,2-benzisothiazol-3(2H)-one 1,1-Dioxide* (**18c**). A soln. of BBr_3 (10.18 g, 3.90 ml, 40.7 mmol) in CH_2Cl_2 (20 ml; dried over 4-Å sieves) was added to a stirred suspension of **18a** (4.75 g, 16.7 mmol) in CH_2Cl_2 (180 ml; dried over 4-Å sieves) under Ar, causing the suspension to dissolve. The soln. was gently refluxed for 4 h, whereby a precipitate was formed; the volatile components were then evaporated. Ice was added to the residue, followed by sat. aq. $NaHCO_3$ soln. (200 ml). This aq. soln. was extracted once with AcOEt (100 ml; org. phase discarded) and then acidified to pH 1 with conc. aq. HCl soln. It was concentrated *in vacuo* to *ca.* ½ of the volume, causing crystallization to start. After some cooling, white crystals of anal. pure **18c** (3.3 g, 92%) were obtained. M.p. 280–282° (dec.). The product may be recrystallized from Et_2O/hexane, if desired. IR: 3400/3310/2684*w*, 1714*s*, 1630/1606/1595/1503*m*. ^{1}H-NMR (80 MHz, (D_6)DMSO): 6.70 (*d*, J = 1.7, 1 H); 6.84 (*d*, J = 1.7, 1 H); 10.0–11.6 (br. 3 H). MS: 215 (M^+), 151 ([$M - SO_2$]$^+$), 136, 124, 108.

11. *2,3-Dihydro-3-oxo-1,2-benzisothiazole-4,6-diyl Diacetate 1,1-Dioxide* (**18d**). Ac_2O (3.44 g, 3.2 ml, 33.4 mmol) was injected to a stirred suspension of **18c** (3.3 g, 15.3 mmol) in dry pyridine (65 ml), causing the suspension

to dissolve. White product started precipitating after 2 h. After a total of 24 h at r.t., the volatile components were removed under high vacuum. The solid residue was triturated with H_2O (10 ml), collected by filtration, and washed with some EtOH. It was then dissolved in H_2O (140 ml) and acidified with 6N aq. HCl, causing the deposit of white crystals of anal. pure **18d** (3.2 g, 70%). M.p. 170–174°. IR: 3184*m*, 1784*s*, 1758*s*, 1607/1595*m*. ^{1}H-NMR (80 MHz (D$_6$)DMSO): 2.28 (*s*, 6 H); 7.49 (*d*, *J* = 1.8, 1 H); 7.92 (*d*, *J* = 1.8, 1 H); 7.68–8.11 (br., 1 H). MS: 299 (M^+), 257 ([$M - C_2H_2O$]$^+$), 215 ([257 – C_2H_2O])$^+$).

12. *Ethyl 2,3-Dihydro-4,6-dimethoxy-3-oxo-1,2-benzisothiazole-2-acetate 1,1-Dioxide* (**26b**). To a soln. of **26a** (3.97 g, 12.6 mmol) in dry DMF (100 ml; from 4-Å sieves) was added finely milled Na_2CO_3 (4.00 g, 37.8 mmol), followed by MeI (17.9 g, 7.8 ml, 126 mmol). The mixture was stirred vigorously for 30 min under Ar and was then poured into H_2O (500 ml). The aq. phase was extracted with AcOEt (3 × 200 ml). The org. phases were dried (Na_2SO_4) and all volatile components removed under high vacuum. The residue was recrystallized once from CH_2Cl_2/hexane, affording white crystals of anal. pure **26b** (3.75 g, 90%). M.p. 166–167°. IR: 1748*s*, 1729*s*, 1613*s*, 1575*s*, 1498*s*. MS: 256 ([$M - CO_2Et$]$^+$), 192, 164.

13. *Methyl 2,4-Dimethoxy-6-*{N-*[(methoxycarbonyl)methyl]sulfamoyl*}*benzoate* (**27**). Under Ar, NaOMe (22.6 ml of 0.554N soln. in MeOH, 12.5 mmol) was added to a suspension of **26b** (3.74 g, 11.4 mmol) in 110 ml of dry MeOH, causing **26b** to dissolve within 10 min. After 3 h, the yellow soln. was quenched with 700 ml of ice/H_2O, and the mixture was acidified with 20 ml of 1N aq. HCl. The product was extracted with AcOEt (4 × 200 ml), dried (Na_2SO_4), and evaporated. On recrystallizing from CH_2Cl_2/Et_2O/hexane, white crystals of anal. pure **27** (2.98 g, 76%) were obtained. M.p. 98–99°. IR: 3264*m*, 2844*m*, 1756*s*, 1746*s*, 1609*s*, 1575*m*, 1494 (sh). MS: 347 (M^+), 315 ([M – MeOH]$^+$), 256 ([315 – CO_2Me]$^+$), 192 ([256 – SO_2]$^+$), 164.

14. *Methyl 4-Hydroxy-5,7-dimethoxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-Dioxide* (**28a**). Under Ar, freshly prepared NaOMe (0.441 N soln. in MeOH, 11.52 mmol) was injected into a flame-dried 100-ml flask. The MeOH was removed under high vacuum, cautiously avoiding any access of air and moisture. Under Ar THF (44 ml, freshly distilled from $LiAlH_4$) was injected to the totally dry NaOMe powder. After 10 min of stirring, high-vacuum-dried **27** (1.00 g, 2.88 mmol) was added in one portion (→ yellow). A yellow solid started precipitating after 15 min of vigorous magnetic stirring at r.t. After 5 h of continued stirring, the mixture was quenched with 0.5N aq. HCl (100 ml) and the aq. phase extracted with AcOEt (3 × 70 ml). After drying (Na_2SO_4) and evaporating, the crude product was chromatographed on silica gel (40 g; benzene/AcOEt 4:1). The purified yellow solid was recrystallized once from AcOEt/hexane: yellow crystals of anal. pure **28a** (0.46 g, 51%). M.p. 198–199°. IR: 3440*m*, 3194*m*, 2848*w*, 1664*s*, 1602*s*. ^{1}H-NMR ((D$_6$)DMSO): 3.90 (*s*, 3 H); 3.97 (*s*, 3 H); 4.00 (*s*, 3 H); 7.00, 7.04 (*AB*, *J* = 1.8, 2 H); 9.82 (*s*, 1 H); 12.11 (*s*, 1 H). MS: 315 (M^+), 256 ([$M - CO_2$Me]$^+$), 251 ([$M - SO_2$]$^+$), 164, 106.

*Methyl 4-Hydroxy-5-methoxy-6-methyl-2*H*-pyrido[4,3-e][1,2]thiazine-3-carboxylate 1,1-Dioxide* (**31a**) was similarly prepared in 72% yield from 2.75 g of **30** (see *Exper. 18*). M.p. 157–158° (dec.). Yellow crystals from AcOEt/Et_2O/hexane, after chromatography over silca gel (AcOEt). IR: 3440*w*, 3220*w*, 1673*s*, 1599/1576/1529*m*. ^{1}H-NMR (80 MHz, (D$_6$)DMSO): 2.61 (*s*, 3 H); 3.88 (*s*, 3 H); 3.93 (*s*, 3 H); 8.76 (*s*, 1 H); 9.8–10.8 (br., 1 H); 11.65 (*s*, 1 H). MS: 300 (M^+), 221, 214, 193.

15. *Methyl 4-Hydroxy-5,7-dimethoxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylate 1,1-Dioxide* (**28b**). Under Ar, NaH (304 mg of a 55% dispersion in oil, 6.98 mmol) was added in 1 portion to a soln. of **28a** (1.10 g, 3.49 mmol) in DMF (40 ml; from 4-Å sieves), and the suspension was stirred vigorously for 1 h at 20°. Under cooling with an ice-bath, MeI (1.98 g, 0.87 ml, 13.96 mmol) was injected. After 15 min of stirring at r.t., the mixture was quenched with H_2O (200 ml) and acidified with 2N aq. HCl. The aq. phase was extracted with AcOEt (4 × 100 ml) the AcOEt phase dried (Na_2SO_4), and all volatile components were evaporated under high vacuum. The resulting semi-solid was recrystallized from AcOEt/hexane, affording yellow crystals of anal. pure **28b** (1.04 g, 90%). M.p. 200–201°. ^{1}H-NMR (80 MHz, (D$_6$)DMSO): very similar to **28a**; additional signal at 2.81 (*s*, 3 H); 9.82 (*s*, 1 H) missing. MS: 329 (M^+), 297 ([M – MeOH]$^+$), 164.

*Methyl 4-Hydroxy-5-methoxy-2,6-dimethyl-2*H*-pyrido[4,3-e][1,2]thiazine-3-carboxylate 1,1-Dioxide* (**31b**) was similarly prepared in 71% yield from **31a** (3.60 g, 12 mmol), NaH (30 mmol), and MeI (18 mmol). White crystals. M.p. 199–200° (dec.) from AcOEt/hexane. IR: 3450*m*, 1656*s*, 1607/1570/1530*m*. ^{1}H-NMR (80 MHz, (D$_6$)DMSO): nearly identical with **31a**; additional signal at 2.93 (*s*, 3 H); 9.8–10.8 (br.) missing. MS: 314 (M^+), 282 ([M – MeOH]$^+$), 214, 207, 183.

16. *4-Hydroxy-5,7-dimethoxy-2-methyl-*N^3*-(pyrid-2-yl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-Dioxide* (**7b**). A soln. of **28b** (1.33 g, 4.43 mmol) and 2-aminopyridine (0.83 g, 8.86 mmol) in *o*-xylene (100 ml) was maintained under reflux with stirring, while a fairly vigorous stream of Ar was bubbled through the soln. Some solvent, along

with the MeOH formed in the aminolysis, was allowed to distill off, and was replaced with new *o*-xylene. After 8 h, the heating was stopped and the product allowed to crystallize for several days: yellow crystals of anal. pure **7b** (0.89 g), after drying under high vacuum at 120°. M.p. 236°. The filtrate was refluxed for another 24 h, while 4/5 of the solvent was allowed to escape by distillation. Crystallization overnight yielded further 0.31 g of pure **7b**. M.p. 237°. Total yield of 1.2 g (69%). IR: 3312*m*, 2638*w*, 1612/1601*s*, 1577*s*, 1526*s*. ^{1}H-NMR ((D$_6$)DMSO): 2.85 (*s*, 3 H); 3.93 (*s*, 3 H); 3.97 (*s*, 3 H); 6.97, 7.01 (*AB*, *J* = 1.8, 2 H); 7.23 (*m*, 1 H); 7.92 (*m*, 2 H); 8.44 (*m*, 1 H); *ca.* 10.3 (br. 1 H); *ca.* 13.6 (br., 1 H). MS: 391 (M^+), 327 ([M – SO_2]$^+$), 233 ([327 – (2-aminopyridine)]$^+$).

*4-Hydroxy-5-methoxy-2,6-dimethyl-*N^3*-(pyrid-2-yl)-2*H*-pyrido[4,3-e][1,2]thiazine-3-carboxamide 1,1-Dioxide* (**31c**) was prepared similarly in 13% yield (0.45 g) from **31b** (2.97 g, 9.45 mmol) and 2-aminopyridine (1.78 g, 18.9 mmol in *o*-xylene (100 ml; black tar in copious amounts was formed in this reaction). Yellow crystals. M.p. 173–176° (dec.) from AcOEt/Et$_2$O/hexane. IR: 3408*m*, 1637*s*, 1577/1498*m*, 1525*s*. ^{1}H-NMR (80 MHz, (D$_6$)DMSO): 2.54 (*s*, 3 H); 2.81 (*s*, 3 H); 3.90 (*s*, 3 H); 7.07 (*m*, 1 H); 7.82 (*m*, 1 H); 8.08 (*m*, 1 H); 8.28 (*m*, 1 H); 8.45 (*s*, 1 H); *ca.* 12.8 (br., 1 H). MS: 376 (M^+), 312 ([M – SO_2]$^+$), 273, 255 ([M – (2-acetamidopyridine)]$^+$), 237, 218 ([312 – (2-aminopyridine)]$^+$), 121 ([PyNHCO]$^+$), 94 ([PyNH$_2$]$^+$).

17. *Ethyl 2,3-Dihydro-4-methoxy-5-methyl-3-oxoisothiazolo[5,4-c]pyridine-2-acetate 1,1-Dioxide* (**29**). To a stirred soln. of the **25c** (3.57 g, 11.9 mmol) in CH_2Cl_2 (40 ml) was added dropwise, while cooling with an ice-bath, diazomethane/Et$_2$O (80 ml, large excess). The solvents were evaporated: 3.65 g of crude **29** as a yellowish oil. Recrystallization from CH_2Cl_2/hexane gave colorless crystals of anal. pure **29** (2.98 g in 3 batches, total 80%). M.p. 125–126°. IR: 1762*s*, 1740*s*, 1584*w*. ^{1}H-NMR (80 MHz, $CDCl_3$): 1.19 (*t*, *J* = 7, 3 H); 2.70 (*s*, 3 H); 4.21 (*s*, 3 H); 4.30 (*q*, *J* = 7, 2 H); 4.43 (*s*, 2 H); 8.84 (*s*, 1 H). MS: 314 (M^+), 241 ([M – CO_2Et]$^+$).

18. *Methyl 3-Methoxy-5-*N*-{[(methoxycarbonyl)methyl]sulfamoyl}-2-methylpyridine-4-carboxylate* (**30**). Under Ar, NaOMe (28.5 ml of 0.31N MeOH soln., 11.1 mmol) was injected to a stirred suspension of **29** (3.70 g, 11.1 mmol) in MeOH (110 ml) causing dissolution of the suspension with yellow color. After 30 min at r.t., the reaction was quenched with H_2O (300 ml). The mixture was neutralized with 1N aq. HCl (10 ml), followed by aqueous buffer of pH 7 (200 ml). The product was extracted with CH_2Cl_2 (4 × 150 ml), dried (Na_2SO_4), and evaporated, affording 3.87 g of methyl/ethyl diester mixture (colorless oil). The transesterification was completed under milder conditions: finely powdered Na_2CO_3 (1.94 g) was added to a soln. of the diester mixture (3.87 g) in MeOH (150 ml), and the suspension was stirred vigorously for 4 h. It was then diluted with H_2O (300 ml) and extracted with CH_2Cl_2 (4 × 150 ml). The org. phase was dried (Na_2SO_4) and evaporated and the yellowish oily residue recrystallized from CH_2Cl_2 hexane: greenish crystals of anal. pure **30** (2.26 g, 58%). M.p. 119–120°. IR: 3100*m*, 1757*s*, 1745*s*, 1584/1560/1499*w*. MS: 332 (M^+), 273 ([M – CO_2Me]$^+$), 244 ([273 – CH_2NH]$^+$), 241 ([273 – MeOH]$^+$), 180 ([244 – SO_2]$^+$).

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