157. *Tilcotil*® Studies
[3+2] Additions with Isothiazol-3(2*H*)-one 1,1-Dioxide

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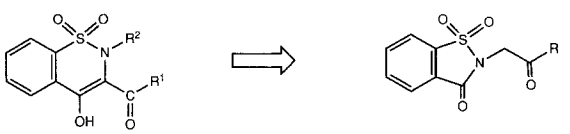
Derivatives of isothiazol-3(2*H*)-one 1,1-dioxide react regiospecifically with 1,3-dipolar agents. The main regiocontrolling factor is ascertained to be the C=O group of the dipolarophile. The topology of the adducts is also in general agreement with predictions based on perturbation theory. Several adducts can be aromatized to heterocyclic equivalents of saccharin, and may then be elaborated into structural analogs of tenoxicam (*Tilcotil*®) and piroxicam (*Feldene*®).

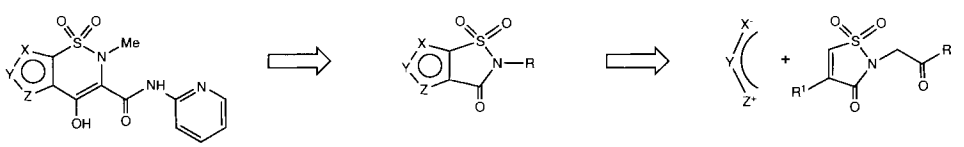
1. Introduction. – The widely used anti-inflammatory drug *Feldene*® (Piroxicam, **1**; *Scheme 1*) and the more recently introduced *Tilcotil*® (Tenoxicam, **2**) are the two best-known representatives of a new class of antirheumatic agents referred to as oxicams [1]. A valuable synthetic approach to oxicams results from an observation by *Abe et al.* [2], *i.e.* that the saccharin derivative **3** (*Scheme 1*) undergoes a methoxide-induced ring enlargement to the thiazinone **4**; the procedure has subsequently been extended [3] to the rearrangement of **5**, which similarly yields **6**. Piroxicam **1** is then obtained from **6** by a chemoselective methylation, affording **7**, followed by aminolysis with 2-aminopyridine [4].

Scheme 1



1 R^1 = 2-Pyridylamino R^2 = Me (Piroxicam, *Feldene*®)
4 R^1 = Ph R^2 = H
6 R^1 = OMe R^2 = H
7 R^1 = OMe R^2 = Me

3 R = Ph
5 R = OMe



2 X = Y = CH Z = S (Tenoxicam, *Tilcotil*®)
8 X = Z = CH Y = S
9 Y = Z = CH X = S
10 X, Y, Z = C, N, O, S, *etc.*

11

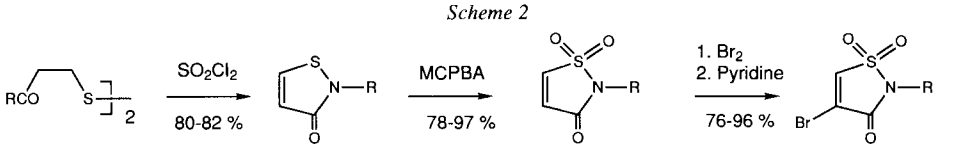
12

13 R^1 = H
14 R^1 = Br

Our own interest in oxicams has always been focussed on heterocyclically annellated thiazines. Thus, besides tenoxicam **2** [5][6], the regioisomers **8** and **9** have been synthesized [6]. Most thiophene-annellated oxicams are at least equipotent to piroxicam; a more general synthetic approach to compounds of the class **10** became, thus, all the more desirable. In analogy to the conversion of **5** to **1**, the heterocyclic saccharin analogs **11** could reasonably be expected to serve as precursors of **10**. Hence, this publication is addressing to the question of whether 'heterocyclic saccharins' (such as **11**) are accessible by adding 1,3-dipoles **12** to a dihydroisothiazole **13** or **14**.

2. Synthesis of the Dipolarophiles 13 and 14. – The synthesis of **13** was carried out as illustrated in *Scheme 2*, using published procedures [7][8]. The amides **15a–c** were readily prepared from 3,3'-dithiodipropionic acid (**15d**), either *via* the acid chloride **15e**, or, preferably in the case of **15a**, *via* the mixed anhydride **15f**. The cyclization to the specific isothiazol-3(2*H*)-one **16** was effected with 3 equiv. of SO_2Cl_2, and the corresponding 1,1-dioxides **13** were conveniently obtained from **16** by peracid oxidation.

Scheme 2



15 a R = $NHCH_2CO_2Et$
b R = NH(*t*-Bu)
c R = $NHCH_2C_6H_4$(*p*-OMe)
d R = OH
e R = Cl
f R = OCO_2Et

16 a R = CH_2CO_2Et
b R = *t*-Bu
c R = $CH_2C_6H_4$(*p*-OMe)

13 a R = CH_2CO_2Et
b R = *t*-Bu
c R = $CH_2C_6H_4$(*p*-OMe)

14 a R = CH_2CO_2Et
b R = *t*-Bu

MCPBA = *m*-Chloroperbenzoic acid

When **13a** or **b** was treated with Br_2 in refluxing CCl_4, the *trans*-4,5-dibromo adducts were formed quantitatively. These could be dehydrobrominated with 1 equiv. of pyridine, affording the 4-bromoderivatives **14**[1]). The methodology outlined above furnished the dipolarophiles **13** and **14** on a 50-g scale.

3. The Isothiazol-3(2*H*)-one 1,1-Dioxides 13 and 14 as Dipolarophiles. – Viewed as electron-deficient dipolarophiles, the compounds **13** and **14** should resemble derivatives of maleic acid, which are known to form adducts with 1,3-dipoles such as diphenylnitrile imine [9], phenyl azide [10], benzonitrile oxide [11], and diazoalkanes [12], in agreement with perturbation-theory analysis [13]. The theory proposes furthermore that, with 'normally'[2]) electron-deficient olefins, these processes should be dipole HO-controlled, except in the nitrile-oxide case, where dipole LU-control would be expected. Most peculiarities of 1,3-dipolar regiocontrol can be rationalized with these premises [13][14];

[1]) Regioisomeric, C(5)-halogenated derivatives were also prepared by a different method. They can be readily differentiated from the C(4)-substituted series by ^{1}H-NMR spectroscopy.

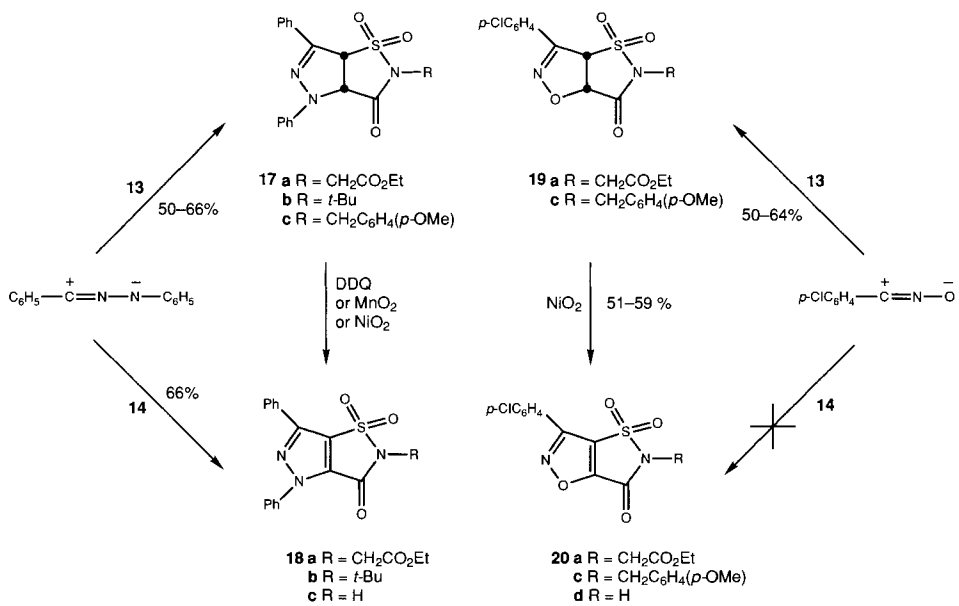
[2]) Regioselectivity of the opposite direction has been predicted for 'strongly' electron-deficient olefins [13].

in fact, for the two reported cases [15][16] of 1,3-dipolar additions to a β-sulfoacrylic-acid moiety typical of **13**, the actually observed selectivities are in agreement with the theory. In practice, the pivotal regiocontrolling factor seems to be simply the C=O group of both **13** and **14**.

3.1. *Addition of Nitrile Imine.* Diphenylnitrile imine adds regiospecifically to **13**, yielding the pyrazoline **17** (*Scheme 3*), under reaction conditions used earlier [9] for simpler acrylates. Any excess of Et_3N must be avoided in this reaction, as it induces eliminating ring opening to pyrazole-5-carboxamide derivatives[3]).

Among many agents examined, only 4,5-dichloro-3,6-dioxocyclohex-1,4-diene-1,2-dinitrile, MnO_2, and NiO_2 were able to dehydrogenate **17** to the aromatic system **18** in low-to-moderate yield. Identical pyrazoles **18** are generated more efficiently by adding nitrile imine to the 4-bromoisothiazolone **14** with *in situ* dehydrobromination (*Scheme 3*).

Scheme 3



3.2. *Addition of Nitrile Oxide.* Considerable ambiguity exists with respect to nitrile-oxide additions to electron-deficient olefins. For acrylates, frontier-orbital analysis predicts dipole LU control with formation of 5-carboxyisoxazolines [13][14]; the experiment proves this adduct to prevail [17], if not to be formed exclusively [11]. Minor alterations in each component may, however, cause the process to shift to dipole HO control, leading to the C(4)-substituted regioisomers [18]. In the case at hand, *p*-chlorobenzonitrile oxide

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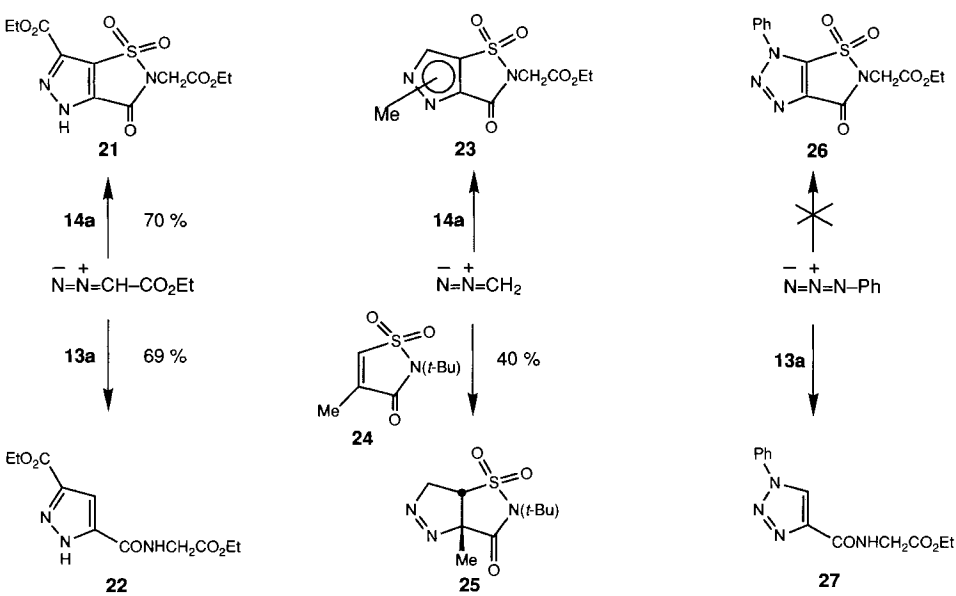
[3]) The adduct **17a**, when treated with 3 equiv. of Et_3N at r.t. in CH_2Cl_2 for 14 h, gave *N*-(1,3-diphenylpyrazole-5-carboxamido)glycine ethyl ester, m.p. 151–152° (76%). Refluxing this amide in 6N HCl for 14 h gave the known [9] 1,3-diphenylpyrazole-5-carboxylic acid, m.p. 228°, in 71% yield.

reacts regiospecifically with **13** to yield the adducts **19**[4]) (*Scheme 3*). Apparently, the sulfonyl group can once more be ignored for the purpose of predicting regioselectivity.

Dehydrogenation to the desired isoxazole **20a** is best carried out with NiO_2 [19] *via* the *p*-methoxybenzyl-protected precursors **19c** and **20c**, and a subsequent ethyl diazoacetate insertion into the acidic saccharin-like N–H bond of compound **20d**[5]).

3.3. *Addition of Diazoalkanes.* Ethyl diazoacetate and CH_2N_2 form labile adducts with **13** and **14** (*Scheme 4*). The adduct of ethyl diazoacetate with **14a** spontaneously aromatizes to the pyrazole **21**[6]) under loss of HBr. The respective adduct with **13a** generates SO_2 *in situ*, yielding the pyrazole-3,5-dicarboxylate **22**[7]). Not surprisingly, dipolar additions of CH_2N_2 to **13** and **14** are difficult to control: the adducts extrude N_2 and SO_2 with ease, and are apt to react further with excess CH_2N_2. Yet, the pyrazole **23** can be obtained in low yield from **14a**[8]), while only decomposition products result from **13b**. Interestingly, the presence of a bridgehead Me group seems to stabilize an adduct such as **25**. The regiospecific course of these diazo additions is identical to the one observed with simple acrylates [23].

Scheme 4



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[4]) The structure was established by an X-ray analysis of the derived **20c**. I thank Mr. *P. Schönholzer, F. Hoffmann-La Roche AG*, Basel, for this work.

[5]) This unfortunate detour is necessitated by the extreme sensitivity of **20a** towards moisture and base, and by the failure of **14** to react with nitrile oxides (*Scheme 3*).

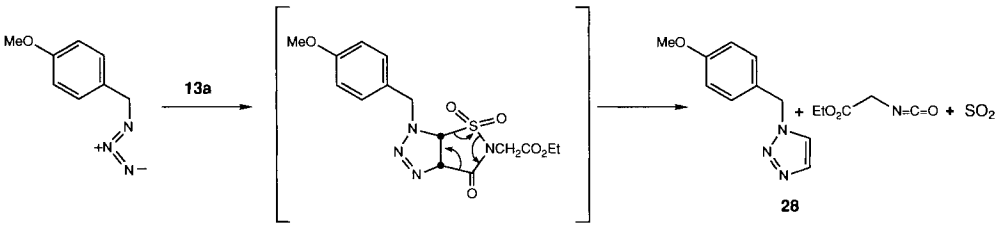
[6]) The structure was established by an X-ray analysis of the derived **31b** (*Scheme 6*). I thank Mr. *P. Schönholzer, F. Hoffmann-La Roche AG*, Basel, for this work.

[7]) For proof, **22** was hydrolyzed with 6N HCl to pyrazole-3,5-dicarboxylic acid, m.p. 298° (reported: 295–297° [20]; 3,4-dicarboxylate: 260° [21]).

[8]) The regio-orientation follows from precedent [22] and from analogy to **21**. ^{1}H-NMR suggests **23** to be a 2:1 mixture of discretely methylated isomers.

3.4. *Addition of Azides.* Our dipolarophiles also react with organic azides, but only at temperatures sufficient to cause extensive decay of the initial dipolar adducts, which cleave off SO_2; the resulting product mixture contains traces of the triazole **27**. The major product proves to be the triazole **28**, generated by the process depicted in *Scheme 5*[9]). No simple adducts with either dihydrotriazole or triazole (**26**, *Scheme 4*) structure have ever been detected in this reaction.

Scheme 5



3.5. *Other 1,3-Dipoles.* Complex mixtures of decomposition products were obtained with azomethine imine (pyridine 1-imide [24]) and with nitrile ylide (benzonitrilium (4-nitrophenyl)methylide [25]). Dipoles essentially unable of generating a heteroaromatic system (such as nitrones) were not examined.

4. Transformation into Oxicams. – The ring-enlargement procedure [3], when applied directly to the precursors **18a**, **20a**, and **21** (*Schemes 3* and *4*), does not give satisfactory results. It can be assumed that the reaction involves opening of the 'saccharin ring' to a diester [26], which then undergoes a *Dieckmann* cyclization to the β-keto-ester **6** (*Scheme 1*). We have found that superior yields are obtained by advancing stepwise, *i.e.* by deliberately opening the 'saccharins' **18a**, **20a**, and **21**, and isolating the intermediate diesters **29**, **30b**[10]), and **31a** (*Scheme 6*). For the subsequent cyclization, the acidic proton in position 1 of **31a** has to be disposed of, most forthrightly in an unexpectedly selective methylation with CH_2N_2, yielding **31b**[6]). The critical *Dieckmann* reaction, leading to heterocyclically annellated oxicams, is preferably carried out in pyridine, using 3.8 equiv. of NaOMe as a base: the keto-esters **32**, **35**, and **37**[11]) are, thus, obtained in up to 87% yield. The dianions derived from **32** and **35** can be *N*-methylated readily with MeI, to afford the keto-esters **33** and **36**, respectively. The final aminolysis of the ester group succeeds only with **33**, producing the illustrative oxicam **34** in 83% yield. Biologically, **34** is much less active than the lead structures **1** and **2**.

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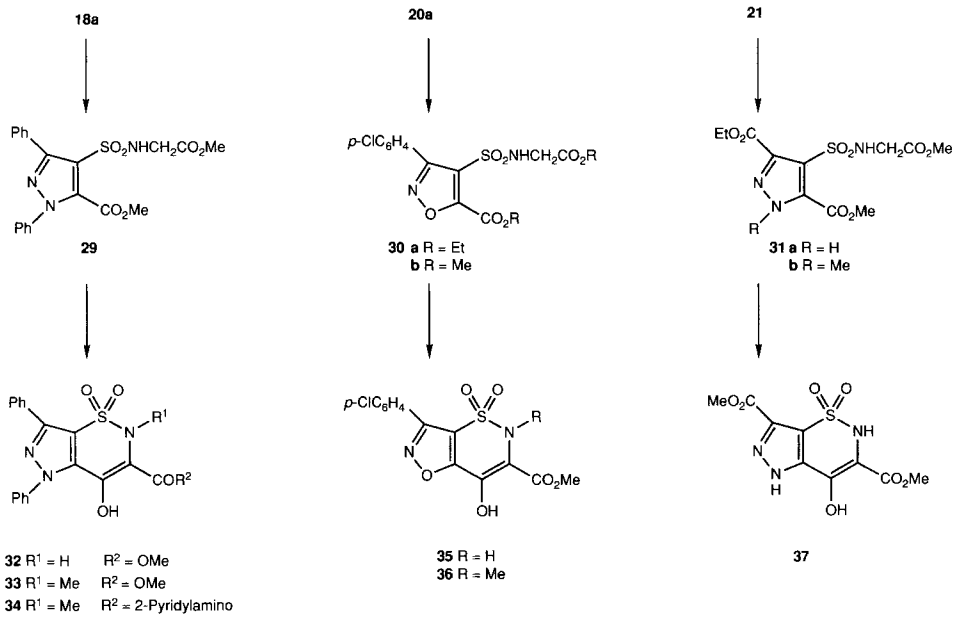
[9]) Full experimental details of this interesting reaction, including the capture of isocyanate, will be presented in a subsequent note.

[10]) As the isoxazoles are very sensitive, especially towards alcoholic base, exposure to methoxide must be minimized, and the thus resulting **30a** then has to be transesterified to **30b** by acid catalysis.

[11]) The recently introduced Me group is apparently lost, concomitant to cyclization.

Scheme 6



5. Conclusion. – Isothiazoles of the type **13** and **14** prove to be versatile intermediates for the synthesis of heterocyclically annellated saccharins, by acting as dipolarophiles in various regiospecific 1,3-dipolar processes. Some of the 'saccharin-like' compounds thus obtained lend themselves to further elaboration into oxicams.

I would like to thank my colleagues of Central Research Units of *F. Hoffmann-La Roche AG,* Basle, for the IR spectra (Mr. *A. Bubendorf*), NMR spectra (Dr. *W. Arnold*), MS (Dr. *W. Vetter* and Mr. *W. Meister*), X-ray analyses (Dr. *J. J. Daly* and Mr. *P. Schönholzer*), 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. were determined on a *Büchi 510* apparatus and are uncorrected. IR spectra: in cm^{-1}, run in KBr, unless stated differently. ^{1}H-NMR spectra: in $CDCl_3$ at 80 MHz unless stated differently, chemical shifts in ppm relative to TMS (= 0 ppm), coupling constants *J* in Hz. Correct elemental analyses were obtained for all compounds.

1. *3,3'-Dithiobis[*N*-alkylpropionamides]* **15a–c.** *3,3'-Dithiobis[*N*-(*p*-methoxybenzyl)propionamide]* (**15c**). A soln. of *3,3'-dithiodipropionyl dichloride* (**15e**) [6] (35.5 g, 143 mmol) in 60 ml of 1,2-dichloroethane was added dropwise over a period of 20 min to a stirred soln. of *p*-methoxybenzylamine (78.7 g, 573 mmol) in 150 ml of 1,2-dichloroethane. A temp. of 30° was maintained with cooling. The precipitate was collected by filtration, and it was purified by stirring it vigorously for 0.5 h as a suspension in two successive 200-ml portions of H_2O. After drying at 80°/14 Torr, 55.7 g (89%) of **15c**. M.p. 185–186° was obtained as a white solid.

Similarly prepared was *3,3'-dithiobis[2-methyl-*N*-(*tert*-butyl)propionamide]* (mixture of diastereoisomers) in 68% yield from the previously described 3,3'-dithiobis(2-methylpropionic acid) [6]. White solid. M.p. 145–170°.

N,N'-*3,3'(Dithiodipropionyl)di(glycine Ethyl Ester)* (**15a**). Under Ar, a soln. of *3,3'-dithiodipropionic acid* (**15d**) (25g, 119 mmol) in 350 ml of DMF (dried over 4-Å molecular sieves) was cooled to –40°, and Et_3N (31.8 ml, 23.1 g, 228 mmol) was added. With stirring at –40°, freshly distilled ethyl chloroformate (21.8 ml, 24.7 g, 228 mmol) was added dropwise over a period of 5 min. After an additional 10 min at –40°, a suspension of vacuum-dried glycine ethyl ester · HCl (31.8 g, 228 mmol) in 350 ml of dried DMF containing 228 mmol (31.8 ml) of Et_3N was added in portions, so that the temp. of the mixture never exceeded –30°. The mixture was stirred for 90 min at –40°, and it was filtered while still cold. The crude product was obtained as a white residue from the filtrate after evaporation of the DMF at high vacuum. The residue was partitioned between CH_2Cl_2 (500 ml) and ice-cold 2M aq. HCl (300 ml), the org. phase was washed with aq. $NaHCO_3$ soln., dried (Na_2SO_4), and the solvents were evaporated under vacuum. The residue was recrystallized once from benzene/Et_2O 1:1, to give 35.1 g (81%) of anal. pure **15a** as white crystals. M.p. 120–121°.

2. *Isothiazol-3(2*H*)-ones* **16**. *2-(p-Methoxybenzyl)isothiazol-3(2*H*)-one* (**16c**). To a stirred suspension of **15c** (30 g, 67 mmol) in 1000 ml of 1,2-dichloroethane was added, at 40° and over a period of 2 h, a soln. of SO_2Cl_2 (16,3 ml, 27.1 g, 200 mmol) in 140 ml of 1,2-dichloroethane. The resulting tan suspension was stirred for additional 2 h at 40°. The solvent was evaporated under vacuum, the residue was dissoved in 600 ml of CH_2Cl_2, and it was washed with H_2O (2 × 150 ml). The org. phase was dried (Na_2SO_4), and the solvent was evaporated under vacuum. The crude product (30 g) was chromatographed on 250 g of silica gel, with CH_2Cl_2/AcOEt (10:1 → 7:3), yielding 27 g of white solid. Recrystallization from CH_2Cl_2/hexane gave 24.3 g (82%) of anal. pure **16c** as white crystals. M.p. 81–82°. IR: 3092*w*, 3072*m*, 2844*w*, 1644*s*, 1585*w*, 1518*s*. MS: 221 (M^+), 121 ([*p*-$MeOC_6H_4CH_2$]$^+$).

Similarly prepared was *2-(*tert*-butyl)-4-methylisothiazol-3(2*H*,4*H*)-one* in 78% yield from *3,3'-dithiobis[2-methyl-*N*-(tert-butyl)propionamide]*: yellowish crystals from pentane. M.p. 83–84°.

*Ethyl [3-Oxo-2*H*-isothiazol-2-yl]acetate* (**16a**). To a soln. of **15a** (28.8 g, 75.8 mmol) in 250 ml of 1,2-dichloroethane was added, dropwise and with stirring at ambient temp., freshly distilled SO_2Cl_2 (30.7 g, 227 mmol) over a period of 90 min. After a total reaction time of 2.5 h, the resulting yellowish soln. was evaporated, and the remaining yellow oil was partitioned between CH_2Cl_2 and aq. $NaHCO_3$ soln. The org. phase was dried (Na_2SO_4) and evaporated. The residue (30 g of yellowish oil) was dissolved in CH_2Cl_2 (75 ml), Et_2O (75 ml) and hexane (40 ml) were added, and the soln. was cooled to –70° with stirring: colorless crystals of anal. pure **16a** (22.7 g, 80%) were collected by cold filtration. M.p. 50–52°. ^{1}H-NMR: 8.20, 6.28 (*AB*, *J* = 7); 4.51 (*s*, 2 H); 4.24 (*dd*, 2 H); 1.28 (*t*, 3 H).

3. *Isothiazol-3(2*H*)-one 1,1-Dioxides* **13**. *Ethyl [3-Oxo-2*H*-isothiazol-2-yl]acetate 1,1-Dioxide* (**13a**). To a stirred soln. of **16a** (25 g, 133 mmol) in 400 ml of CH_2Cl_2, over 30 min, *m*-chloroperbenzoic acid (*Fluka pract.*, 90%; 50.7 g, 293 mmol) was added in portions, while the temp. was kept below 20° by cooling with ice. After 15 h of stirring at r.t., the precipitated *m*-chlorobenzoic acid was removed by filtration, and the filtrate was extracted twice with aq. $NaHCO_3$ soln. The org. phase was dried (Na_2SO_4), and the solvent evaporated under vacuum. The product was crystallized from CH_2Cl_2/hexane, yielding anal. pure **13a** (23 g, 78%) as white crystals. M.p. 74–74.5°. IR: 3092*s*, 1744*s*, 1586*m*, 1340 and 1175*s* (SO_2). ^{1}H-NMR: 7.53, 6.87 (*AB*, *J* = 7.5); 4.33 (*s*, 2 H); 4.27 (*dd*, 2 H); 1.30 (*t*, 3 H). MS: 219 (M^+), 174 (M^+ – OEt), 146 (M^+ – CO_2Et), 119 (146 – HCN).

Similarly prepared were: *2-(*tert*-butyl)isothiazol-3(2*H*)-one 1,1-dioxide* (**13b**), white crystals in 97% yield from **16b** [6], m.p. 78–80°, and *2-(*p*-methoxybenzyl)isothiazol-3(2*H*)-one 1,1-dioxide* (**13c**): yellowish crystals in 88% yield from **16c**, m.p. 96–97°.

4. trans-*4,5-Dibromo-4,5-dihydroisothiazol-3(2*H*)-one 1,1-Dioxides. Ethyl [*trans-*4,5-Dibromo-4,5-dihydro-3-oxo-2*H*-isothiazol-2-yl]acetate 1,1-Dioxide*. Br_2 (80,0 g, 500 mmol) was added dropwise to a stirred suspension of **13a** (50.0 g, 228 mmol) in 1500 ml of CCl_4 at r.t., and the resulting mixture was then refluxed for 20 h. Most of the solvent, along with the excess Br_2, was evaporated under vacuum. The product crystallized from the remaining *ca.* 300 ml of CCl_4: white crystals of anal. pure compound. M.p. 132–134° (74.2 g, 86%). ^{1}H-NMR: 5.44, 4.99 (*AB*, *J* = 7.5). MS: 306/305/304 (M^+ – CO_2Et), 226/224 (M^+ – CO_2Et – HBr).

Similarly prepared was *2-(*tert*-butyl)-4,5-*trans*-dibromo-4,5-dihydroisothiazol-3(2*H*)-one 1,1-dioxide* in quant. yield from **13b**, white crystals from CCl_4/hexane. M.p. 94–96°. IR: 1738*s*.

5. *4-Bromoisothiazol-3(2*H*)-one 1,1-Dioxides* **14**. *Ethyl [4-Bromo-3-oxo-2*H*-isothiazol-2-yl]acetate 1,1-Dioxide* (**14a**). A soln. of pyridine (6.3 g, 80 mmol) in 70 ml of $CHCl_3$ was added dropwise to a stirred soln. of

ethyl (*trans*-4,5-dibromo-4,5-dihydro-3-oxo-2*H*-isothiazol-2-yl)acetate 1,1-dioxide (28.2 g, 74.5 mmol) in 350 ml of $CHCl_3$ at 20°. After 2.5 h, the soln. was washed with H_2O (2 × 150 ml). The org. phase was dried (Na_2SO_4), the solvent was evaporated under vacuum, and the residual brown oil was filtered over 150 g of silica gel. Elution with CH_2Cl_2 afforded 22 g of colorless oil, which was recrystallized from Et_2O/hexane, to yield white crystals of **14a** (19.5 g, 88%). M.p. 64–65°. IR: 3076*m*, 1763*s*, 1746*s*, 1590*m*, 1345/1335*s*, 1235*s*, 1177*s*. ^{1}H-NMR: 7.68 (*s*, 1 H); 4.37 (*s*, 2 H); 4.23 (*dd*, 2 H); 1.32 (*t*, 3 H). MS: 297 (M^+), 252 (M^+ – OEt), 224 (M^+ – CO_2Et).

Similarly prepared was *4-bromo-2-(*tert*-butyl)isothiazol-3(2*H*)-one 1,1-dioxide* (**14b**), white crystals from CH_2Cl_2/hexane in 96% yield from 4,5-*trans*-dibromo-2-(*tert*-butyl)-4,5-dihydroisothiazol-3(2*H*)-one 1,1-dioxide. M.p. 144–146°. IR: 3070*s*, 1734*s*, 1611*m*. MS: 252 (M^+ – CH_3).

6. *1,3-Dipolar Additions with* **13** *as the Dipolarophile.* 6.1. *Reaction with Nitrile Imine.* cis-*4,6a-Dihydro-2-(4-methoxybenzyl)-4,6-diphenyl-2*H*-pyrazolo[3,4-*d*]isothiazol-3(3a*H*)-one 4,4-Dioxide* (**17c**). The dipolarophile **13c** (1.27 g, 5 mmol) was dissolved in 30 ml of CH_2Cl_2, and *N*-phenylbenzenehydrazonoyl chloride [9] (1.5 g, 6.5 mmol) was added. The suspension was stirred at r.t., while Et_3N (0.56 g, 6.5 mmol) was added dropwise. From the resulting clear soln., the product started precipitating after *ca.* 1 h. After 5 h of stirring, the mixture was poured into 250 ml of 0.1M HCl, and the product was first extracted with CH_2Cl_2 (150 ml) then with AcOEt (3 × 100 ml). The org. phases were dried (Na_2SO_4), combined, and the solvents were evaporated under vacuum. The crude product (2.35 g of reddish powder) was recrystallized from acetone/hexane to yield 1.47 g (66%) of anal. pure **17c** as yellowish crystals. M.p. 152° (dec.). IR: 2844*w*, 1734*s*. ^{1}H-NMR ((D_6)DMSO): 7.93–6.75 (*m*, 14 H); 6.40, 5.84 (*AB*, *J* = 11.5); 4.71 (*s*, 2 H); 3.73 (*s*, 3 H). CI-MS (with NH_4^+): 384 (M^+ + H – SO_2), 221 ([1,3-diphenylpyrazolium]$^+$).

Similarly prepared were *ethyl [*cis-*3,3a,4,6a-tetrahydro-4,6-diphenyl-2*H*-pyrazolo[3,4-*d*]isothiazol-2-yl]acetate 1,1-dioxide* (**17a**): pale yellow crystals from CH_2Cl_2/hexane in 50% yield from **13a**. M.p. 132–132.5° (dec.) and *2-(*tert*-butyl)-4,6a-dihydro-4,6-diphenyl-2*H*-pyrazolo[3,4-*d*]isothiazol-3(3a*H*)-one 1,1-dioxide* (**17b**): pale-yellow crystals from CH_2Cl_2/hexane in 63% yield from **13b**. M.p. 194° (dec.).

6.2. *Reaction with Nitrile Oxide.* cis-*3-(4-Chlorophenyl)-3a,6a-dihydro-5-(*p*-methoxybenzyl)-isothiazolo[5,4-*d*]isoxazol-6(5*H*)-one 4,4-Dioxide* (**19c**). To a soln. of **13c** (12.0 g, 47.5 mmol) and 4-chloro-*N*-hydroxybenzenecarboximidoyl chloride (12.0 g, 63.0 mmol) in a mixture of CH_2Cl_2 (40 ml) and benzene (240 ml), Et_3N (6.35 g, 63.0 mmol) was added dropwise under stirring, while internal temp. of 20° was maintained by cooling. Minutes after the completed addition, the crude product started precipitating. After 3 h of stirring, the product was collected by filtration, washed with H_2O (250 ml), and dried at 60° under vacuum, to yield a pale yellow solid of **19c** (12.3 g, 64%), which was sufficiently pure for the subsequent dehydrogenation. Anal. pure **19c** was obtained by recrystallizing from CH_2Cl_2/hexane: white crystals. M.p. 245–246°. IR: 2840*w*, 1724*s*. ^{1}H-NMR ((D_6)DMSO): 6.50, 6.05 (*AB*, *J* = 10, H–C(3a), H–C(6a)). MS: 406 (M^+), 342 (M^+ – SO_2), 180.

Similarly prepared was *ethyl [*cis-*6-(*p*-chlorophenyl)-6,6a-dihydro-3-oxo-2*H*-isoxazolo[4,5-*d*]isothiazol-2-yl]acetate 1,1-dioxide* (**19a**): white crystals from CH_2Cl_2/hexane in 54% yield from **13a**. M.p. 180–181°. IR: 1763*s*. ^{1}H-NMR: 5.90, 5.71 (*AB*, *J* = 10.5, H–C(3a), H–C(6a)). MS: 372 (M^+), 308 (M^+ – SO_2).

6.3. *Reaction with Diazoalkanes. Ethyl 5-{[(Ethoxycarbonyl)methyl]carbamoyl}-1*H*-pyrazole-3-carboxylate* (**22**). Ethyl diazoacetate (1.64 g, 14.4 mmol) was added dropwise to a stirred soln. of **13a** (3.0 g, 13.7 mmol) in 60 ml of benzene. After 1 h at r.t., the soln. was kept at 60° for 14 h, whereby the product was precipitated. Anal. pure **22** (2.54 g, 69%) could be collected by filtration as white crystals. M.p. 154–155°). IR: 3394*m*, 3220*m*, 3144*m*, 1762*s*, 1708*s*, 1664*s*, 1552*s*. MS: 269 (M^+), 224 (M^+ – OEt), 196 (M^+ – CO_2Et), 167, 121.

cis-*2-(*tert*-Butyl)-3a,6a-dihydro-3-methyl-2*H*-pyrazolo[3,4-*d*]isothiazol-4(6*H*)-one 1,1-Dioxide* (**25**). Ethereal CH_2N_2 soln. (10 ml, large excess) was added at 0° to a soln. of **24** (100 mg, 0.49 mmol) in 3 ml of CH_2Cl_2, and the mixture was stored at 0° for 3 d. The solvents were evaporated, the remaining white solid was dissolved in 2 ml of THF, and 2 ml of 0.5M aq. HCl was added. After 15 min, the mixture was partitioned between CH_2Cl_2 and sat. $NaHCO_3$ soln., the org. phase was dried (Na_2SO_4), and the solvents were evaporated under vacuum, to yield 99 mg of crude product. On recrystallizing from CH_2Cl_2/hexane, anal. pure **25** (48.6 mg, 40%) was obtained. M.p. 159–160°. IR: 1715*s*, 1554*s*, 1339*s*, 1303*s*, 1156*s*. ^{1}H-NMR: *ABX* systems: 5.61 (*dd*, J_1 = 19.2, J_2 = 2.9); 5.03 (*dd*, J_1 = 19.3, J_3 = 8.3); 3.59 (*dd*, J_2 = 2.9, J_3 = 8.3); 1.79 (*s*, 3 H); 1.65 (*s*, 9 H).

6.4. *Reaction with Azides. 1-(4-Methoxybenzyl)-1*H*-1,2,3-triazole* (**28**). A soln. of **13a** (1.31 g, 6.0 mmol) and of 1-(azidomethyl)-4-methoxybenzene [27] (1.46 g, 9 mmol) in 15 ml of toluene was kept at 100° for 2 h. The toluene was evaporated under vacuum, and the residue was chromatographed on 60 g of silica gel with CH_2Cl_2/AcOEt 9:1. Anal. pure **28** was collected as a white solid (0.79 g, 70%). IR: 3102*s*, 2842*w*, 1611*s*, 1586*m*, 1516*s*, 1484*m*. ^{1}H-NMR: *AB* systems: 7.75 (*d*, *J* = 1, 1 H); 7.52 (*d*, *J* = 1, 1 H); *AA'BB'* systems: 7.27 (*m*, 2 H); 6.98 (*m*, 2 H); 5.54 (*s*, 2 H); 3.83 (*s*, 3 H). MS: 189 (M^+), 161 (M^+ – N_2), 121 ([4-methoxybenzyl]$^+$).

7. *1,3-Dipolar Additions with* **14** *as the Dipolarophile.* 7.1. *Reactions with Nitrile Imine. Ethyl [3,4-Dihydro-3-oxo-4,6-diphenyl-2*H*-pyrazolo[3,4-*d*]isothiazol-2-yl]acetate 1,1-Dioxide* (**18a**). The dipolarophile **14a** (8.22 g, 27.6 mmol) was dissolved in 100 ml of CH_2Cl_2, and *N*-phenylbenzenehydrazonoyl chloride [9] (9.54 g, 41.4 mmol) was added. The suspension was cooled to –20°, and with stirring, Et_3N (6.98 g, 69 mmol) was added over a period of 5 min. The cooling bath was removed, and the brown suspension was kept stirring, while it reacted as it dissolved. After 45 min, the soln. was poured onto 200 ml of 0.05M aq. HCl, and the product was extracted into CH_2Cl_2. The org. phase was dried (Na_2SO_4) and evaporated. The resulting 15.3 g of dark oil was chromatographed with CH_2Cl_2 on 200 g of silica gel, to yield 8.1 g of a reddish semi-solid. On recrystallization from CH_2Cl_2/hexane, anal. pure **18a** (7.44 g, 66%) was obtained as yellowish crystals. M.p. 159–160°. IR: 1755*s*, 1740*s*, 1504*m*, 1340*s*, 1170*s*. MS: 411 (M^+), 338 ($M^+ - CO_2Et$), 247, 77.

Similarly prepared was *2-(*tert*-butyl)-3,4-dihydro-4,6-diphenyl-2*H*-pyrazolo[3,4-*d*]isothiazol-3(4*H*)-one 1,1-dioxide* (**18b**) in 68% yield from **14b**. M.p. 206°. IR: 1726*s*, 1510*s*, 1335*s*, 1160*s*. ^{1}H-NMR: 7.95 (*m*, 4 H); 7.43 (*m*, 6 H); 1.80 (*s*, 9 H). MS: 381 (M^+), 366 ($M^+ - CH_3$), 325 ($M^+ - C_4H_8$).

7.2. *Reactions with Diazoalkanes. Ethyl [6-(Ethoxycarbonyl)-3,4-dihydro-3-oxo-2*H*-pyrazolo-[3,4-*d*]isothiazol-2-yl]acetate 1,1-Dioxide* (**21**). The dipolarophile **14a** (2 g, 6,7 mmol) was dissolved in 50 ml of CH_2Cl_2, and 1 ml of ethyl diazoacetate was added. After 5 min of reacting at r.t., the soln. was evaporated to dryness, while the flask was heated to 50°. (Warning: both educts and the product appear to be explosive.) This process was repeated 5 ×, for a total utilization of 12 g of **14a**. The combined crude products were chromatographed on 100 g of silica gel. On eluting with CH_2Cl_2, 3.8 g of pure **14a** was recovered. Subsequently with AcOEt, chromatographically pure **21** (7 g) was eluted. Recrystallization from CH_2Cl_2/hexane afforded colorless crystals of anal. pure **21** (6.4 g, 70%). M.p. 128–129°. IR: 3286*s*, 1766*s*, 1757*s*, 1593*m*. MS: 258 ($M^+ - CO_2Et$), 230 ($258 - C_2H_4$), 194 ($258 - SO_2$).

*Ethyl [3,4-Dihydro-4-(and-5-)methyl-3-oxo-2*H*-pyrazolo[3,4-*d*]isothiazol-2-yl]acetate 1,1-Dioxide* (**23**). Ethereal CH_2N_2 soln. (25 ml, large excess) was added to a soln. of **14a** (500 mg, 1.68 mmol) in 17.5 ml of CH_2Cl_2 at –20°. After 30 min, Et_3N (0.234 ml, 1.68 mmol) was added, and the soln. was allowed to warm to r.t. The solvents were then evaporated without further warming, and the residual oil was partitioned between CH_2Cl_2 and H_2O. The org. phase was dried (Na_2SO_4), evaporated, and the residue was triturated with Et_2O. The Et_2O-soluble part was diluted with hexane and allowed to crystallize. Anal. pure **23** (165 mg, 36%) was collected as a 4:1 mixture of 4-methyl and 5-methyl derivatives. M.p. 86–114°. The major component, presumably the 4-methylated isomer of **23**, can be obtained in pure form by repeatedly crystallizing from Et_2O/hexane: white crystals. M.p. 102–104°. IR: 3150*w*, 1764*s*, 1756*s*, 1509*m*. ^{1}H-NMR: 7.80 (*s*, 1 H). MS: 273 (M^+), 237, 200 ($M^+ - CO_2Et$).

8. *Dehydrogenation of the Dipole Adducts* **17** *and* **19**. *2-(*tert*-Butyl)-3,4-dihydro-4,6-diphenylpyrazolo-[3,4-*d*]isothiazol-3(2*H*)-one 1,1-Dioxide* (**18b**; see also *6.7.1*). To a soln. of **17b** (800 mg, 2.08 mmol) in 40 ml of CH_2Cl_2 was added in portions, with vigorous stirring at r.t., NiO_2 [19] (3.20 g). After 4 d of continued stirring, the metal salts were removed by filtration, and the filtrate was evaporated, leaving 700 mg of brown crude product. Recrystallization from CH_2Cl_2/hexane afforded anal. pure **18b** (230 mg, 30%). M.p. 206° (for spectroscopic data, see *6.7.1*).

*3-(4-Chlorophenyl)-5-(4-methoxybenzyl)isothiazolo[5,4-*d*]isoxazol-6(5*H*)-one 4,4-Dioxide* (**20c**). To a soln. of **19c** (3.1 g, 7.62 mmol) in in 550 ml of CH_2Cl_2 was added in portions, with vigorous stirring at r.t., NiO_2 [19] (9 g), and the stirring was continued for 3 h; then the metal salts were removed by filtration, and the solvent was evaporated *in vacuo*. This process was repeated 4 ×, for a total utilization of 15.5 g of **19c**. The combined crude products were triturated with 50 ml of CH_2Cl_2, whereby 5.5 g of unreacted starting material remained undissolved, and could be collected by filtration. The soluble part was chromatographed on 120 g of silica gel, with CH_2Cl_2: 5.5 g of chromatographically pure **20c** were first collected, followed by 0.7 g of unreacted **19c**. The product was recrystallized from CH_2Cl_2/hexane, giving colorless crystals of anal. pure **20c**[4]) (4.7 g, 51% calculated yield, based on 9.3 g of starting material converted). M.p. 145–147°. IR: 2844*w*, 1758*s*, 1594*s*, 1518*s*, 1352*s*. MS: 404 (M^+), 121 ($[MeOC_6H_4CH_2]^+$).

Compound **18a** (see also *7.1*). To a soln. of **17a** (610 mg, 1.47 mmol) and 75 mg of conc. H_2SO_4 in 30 ml of THF 2,3-dichloro-5,6-dicyanobenzoquinone (402 mg, 1.77 mmol) was added, and the resulting green soln. was heated to reflux with stirring, whereby the color changed to dark brown. After 2 h, the soln. was evaporated to *ca.* 10 ml, and it was partitioned between sat. aq. $NaHCO_3$ soln. (70 ml) and CH_2Cl_2 (70 ml). After drying with Na_2SO_4 and evaporating, the crude product was chromatographed (30 g of silica gel, CH_2Cl_2). Recrystallization from CH_2Cl_2/hexane afforded pure **18a** (150 mg, 25%). For anal. data, see *7.1*.

9. *Removal of the* tert-*Butyl and the* p-*Methoxybenzyl Protecting Groups. 3,4-Dihydro-4,6-diphenylpyrazolo[3,4-*d*]isothiazol-3(2H)-one 1,1-Dioxide* (**18c**). A soln. of 170 mg of **18b** in 8 ml of CF_3COOH was maintained at reflux for 2 d. The acid was then evaporated under vacuum, and the residue was repeatedly evaporated from an AcOEt soln. Recrystallization from AcOEt/hexane finally gave anal. pure **18c** (66 mg, 46%) as white crystals. M.p. 213–214°. IR: 3128*w*, 3018*w*, 2728*w*, 1730*s*, 1579*m*, 1531*m*, 1500*m*, 1485*m*, 1345*s*, 1310*s*, 1172*s*. MS: 325 (M^+), 218 ($M^+ - SO_2 - CONH$).

*3-(4-Chlorophenyl)isothiazolo[5,4-*d*]isoxazol-6(5H)-one 4,4-Dioxide* (**20d**). A suspension of **20c** (5.8 g, 14.3 mmol) and anisole (9.28 g, 9.3 ml, 86 mmol) in 145 ml of CF_3COOH was maintained at 60° for 20 h with stirring. A pink soln. was formed initially, from which an orange solid was slowly precipitated. The acid was evaporated under vacuum, and the residue was partitioned between 10% aq. $NaHCO_3$ soln. (1200 ml) and Et_2O (1200 ml). The aq. phase was acidified with conc. HCl soln., and the thus precipitated **20d** (3.8 g, 93%) was collected by filtration, washed with H_2O, and dried at 80° under high vacuum. Bright yellow powder. M.p. 250–256° (dec.).

10. N-*Alkylation of* **20d** *with Ethyl Diazoacetate. Ethyl [3-(*p-*Chlorophenyl)-6-oxo-5H-isothiazolo[5,4-*d*]isoxazol-5-yl]acetate 4,4-Dioxide* (**20a**). A $CHCl_3$ suspension (195 ml) containing **20d** (2.44 g, 8.57 mmol) and ethyl diazoacetate (3.92 g, 3.6 ml, 34.4 mmol) was slowly heated to 60° with stirring. The solid was gradually dissolving, as it reacted with the diazoester, forming a yellow soln. After 2.5 h, the solvent was evaporated under vacuum, and the resulting yellow oil was recrystallized from Et_2O, yielding anal. pure **20a** (1.8 g, 56%) as yellow crystals. M.p. 139–141°. IR: 3000*w*, 2955*w*, 1773*s*, 1760*s*, 1602*m*, 1573*w*, 1447*m*, 1371*s*, 1178*s*. MS: 370 (M^+), 297 ($M^+ - CO_2Et$), 271 ($M^+ - NCCO_2Et$), 179 (271 – SO_2 – CO). A less pure second fraction of m.p. 122–138° (0.7 g, 22%) can be crystallized from the ethereal filtrate; it contains some of the isomeric *O*-alkylated product ('*ethyl [3-(*p-*chlorophenyl)-6-hydroxyisothiazolo[5,4-*d*]isoxazol-6-yl]acetate 4,4-dioxide*').

11. *Methoxide-Induced Opening of the 'Saccharin' Ring. Methyl 4-{[(Methoxycarbonyl)methyl]sulfamoyl}-1,3-diphenylpyrazole-5-carboxylate* (**29**). A 0.61M soln. of NaOMe in MeOH (22.9 ml, 14.0 mmol) was injected into a suspension of **18a** (5.75 g, 14.0 mmol) in 290 ml of Et_2O during 10 min, while maintaining a temp. of 20° by means of external cooling and stirring. A yellow soln. was obtained after 5 min, from which a product (presumably the Na salt of **29**) started to crystallize immediately. After 15 min, the product mixture was poured into 400 ml of H_2O. HCl (105 ml of 1M aq. soln.) was added, and the product was extracted into CH_2Cl_2 (3 × 200 ml). After drying (Na_2SO_4) and evaporation of the solvents, 5.6 g of white powder was obtained. On recrystallizing once from CH_2Cl_2/hexane, white crystals of anal. pure **29** (5.4 g, 90%) could be collected. M.p. 169–170°. IR: 3281*s*, 1747*s*, 1583*m*, 1525*m*, 1495*m*, 1338*s*, 1152*s*. MS: 429 (M^+), 397 (M^+ – MeOH), 370 ($M^+ - CO_2Me$), 341 (370 – CH_2NH), 338 (370 – MeOH).

Ethyl 4-{[(Methoxycarbonyl)methyl]sulfamoyl}-5-(methoxycarbonyl)pyrazole-3-carboxylate (**31a**). A 0.59M soln. of NaOMe (28.1 ml, 16.5 mmol) in MeOH was injected into a soln. of **21** (2.6 g, 7.85 mmol) in 100 ml of MeOH. After 15 min at 20°, the MeOH was evaporated under vacuum, and the residue was quenched with 200 ml of aq. buffer (pH 3) soln. The product was extracted into AcOEt (4 × 100 ml), the org. phase dried (Na_2SO_4), and the solvent evaporated. Recrystallization from CH_2Cl_2/hexane gave white crystals of anal. pure **31a** (2.20 g, 85%). M.p. 102–103°.

*Ethyl 3-(*p-*Chlorophenyl)-4-{[(ethoxycarbonyl)methyl]sulfamoyl}isoxazole-5-carboxylate* (**30a**). A 0.63M soln. of NaOEt (15.9 ml, 10.0 mmol) in EtOH was slowly injected at 0° into a stirred suspension of **20a** (3.7 g, 10 mmol) in 200 ml of dry Et_2O. The resulting yellow soln. was kept at 0° for 1.5 h, and it was then quenched with 100 ml (10 mmol) of aq. 0.1M HCl soln. The ethereal phase was collected, the aq. phase extracted with CH_2Cl_2, and the combined org. phases were dried (Na_2SO_4) and evaporated. Chromatography with CH_2Cl_2 on 120 g of silica gel gave spectroscopically pure **30a** (3.6 g, 87%) as a colorless oil. Anal. pure material crystallized from Et_2O/pentane: colorless crystals. M.p. 44–46°. IR: 3340*w*, 1753*s*, 1604*m*, 1350*s*, 1186*s*,1150*s*. MS: 416 (M^+), 343 ($M^+ - CO_2Et$), 297 (343 – EtOH).

12. *Regioselective Methylation of* **31a** *with* CH_2N_2. *3-Ethyl 4-{[(Methoxy-carbonyl)methyl]sulfamoyl}-1-methyl-5-(methoxycarbonyl)pyrazole-3-carboxylate* (**31b**). Ethereal CH_2N_2 soln. (*ca.* 15 ml) was added dropwise to a stirred and cooled (–20°) soln. of **30a** (2.0 g, 5.73 mmol) in 40 ml of CH_2Cl_2, until the yellowish CH_2N_2 tint was no longer vanishing. The solvents were then evaporated under vacuum, and the residual colorless oil was recrystallized from AcOEt/Et_2O, yielding chromatographically pure **30b** (1.7 g, 82%) as white crystals. M.p. 85–95°. Anal. pure and totally isomer-free **30b**[6]) could be obtained after one further crystallization from AcOEt/Et_2O. M.p. 98–99.5°. IR: 3284*m*, 1753*s*, 1722*s*, 1520*w*. MS: 364 (M^+ + H), 332 (M^+ – MeO), 318 (M^+ – EtO), 304 ($M^+ - CO_2Me$), 275 (304 – CH_2NH), 272 (304 – MeOH), 258 (M^+ – EtOH).

13. *Transesterification of* **30a**. *Methyl 3-(*p*-Chlorophenyl)-4-{[(methoxycarbonyl)methyl]-sulfamoyl}isoxazole-5-carboxylate* (**30b**). A soln. of **30a** (3.95 g, 9.47 mmol) and 1.0 ml of conc. H_2SO_4 in 200 ml of MeOH was maintained at reflux for 4 d. The soln. was evaporated to *ca.* 20 ml *in vacuo* and then partitioned between H_2O and CH_2Cl_2. The org. phase was dried (Na_2SO_4), evaporated, and chromatographed (200 g of silica gel, CH_2Cl_2). The chromatographically pure product was finally recrystallized from Et_2O/pentane, affording anal. pure **30b** (3.0 g, 82%) as colorless crystals. M.p. 74–76°. IR: 3372*m*, 1753*s*, 1607*m*, 1357*s*, 1186*s*,1153*s*. MS: 388 (M^+), 329 ($M^+ - CO_2Me$), 300 (329 – CH_2NH).

14. *Synthesis of Oxicams* via *the* Dieckmann *Reaction. Methyl 1,5-Dihydro-7-hydroxy-1,3-diphenylpyrazolo[3,4-*e*][1,2]thiazine-6-carboxylate 4,4-Dioxide* (**32**). Dry pyridine (107 ml) was injected into a dry flask containing NaOMe powder (1.90 g, 35.1 mmol). While maintaining under Ar, **29** (4.0 g, 9.3 mmol) was added in one portion, and the mixture was stirred vigorously for 7 h at 45°, while the soln. changed color from yellow to red. The pyridine was then evaporated at high vacuum with only slight warming. The remaining orange solid was dissolved in 170 ml of H_2O, and the soln. was acidified with 2M aq. HCl soln. The white precipitate was collected by filtration, dissolved in CH_2Cl_2, dried (Na_2SO_4), and evaporated, leaving 2.95 g of white powder. It was recrystallized once from 300 ml of AcOEt, giving yellow crystals of anal. pure **32** (2.6 g, 70%). M.p. 249–250°. IR: 3440*w*, 3194*w*, 1669*s*,1616*m*, 1498*s*, 1351*s*, 1312*s*, 1168*s*, 1146*s*. MS: 397 (M^+), 339, 310, 247.

Similarly prepared were *methyl 3-(*p*-chlorophenyl)-7-hydroxy-5*H*-isoxazolo[5,4-*e*][1,2]thiazine-6-carboxylate 4,4-dioxide* (**35**; yellow crystals from AcOEt/hexane. M.p. 213–215°) by reacting with NaOMe for 22 h at 20°, in 54% yield from **30b** (IR: 3420*w*, 3220*s*, 1691*s*, 1618*w*, 1602*m*, 1589*m*, 1573*m*, 1515*w*, 1334*s*, 1152*s*; MS: 356 (M^+)) and *dimethyl 2,5-dihydro-4-hydroxypyrazolo[3,4-*e*][1,2]thiazine-3,7-dicarboxylate 1,1-dioxide* (**37**) by reacting with NaOMe for 18 h at 50°, in 36% yield from **31b** (pale yellow crystals from AcOEt. M.p. 238° (dec.). IR: 3400*w*, 3133*m*, 2640*w*, 1723*s*, 1684*s*, 1605*m*. MS: 303 (M^+)).

15. *Regiospecific Monomethylation of Oxicams. Methyl 1,5-Dihydro-7-hydroxy-5-methyl-1,3-diphenylpyrazolo[3,4-*e*][1,2]thiazine-6-carboxylate 4,4-Dioxide* (**33**). Under Ar, vacuum pre-dried **32** (3.4 g, 8.6 mmol) was dissolved in dry DMF (133 ml). NaH (0.75 g of a 55% dispersion in oil, 17.2 mmol) was added in one portion, and the mixture was stirred at 20° for 1 h, while its color changed from yellow *via* orange to red. MeI (2.15 ml, 4.9 g, 34.5 mmol) was then injected, causing immediate fading of the red color. After 10 min, the yellowish mixture was poured onto 150 ml of ice H_2O, and the soln. was acidified with 2M HCl soln. The white precipitate was collected, and it was washed with hexane (3 × 8 ml) in order to remove the mineral oil. The remaining white solid was dissolved in CH_2Cl_2, dried (Na_2SO_4), and then evaporated, leaving 3.7 g of slowly crystallizing oil. It was recrystallized once from AcOEt/hexane, yielding anal. pure **33** (3.0 g, 85%) as yellowish crystals. M.p. 188–190° (purest **33** melts at 189–191°). IR: 3070*w*, 1665*m*, 1597*m*, 1498*m*, 1352/1167*s*. ^{1}H-NMR: 11.95 (*s*, 1 H); 8.09 (*m*, 2 H); 7.55 (*m*, 8 H); 3.96 (*s*, 3 H); 3.14 (*s*, 3 H). MS: 411 (M^+), 347 ($M^+ - SO_2$), 345, 247.

Similarly prepared was *methyl 3-(*p*-chlorophenyl)-7-hydroxy-5-methyl-5*H*-isoxazolo[5,4-*e*][1,2]thiazine-6-carboxylate 4,4-dioxide* (**36**) in 69% yield from **35** (yellowish crystals from AcOEt/hexane. M.p. 210° (dec.). IR: 1676*m*, 1605*m*, 1573*w*, 1514*w*, 1366/1175*s*. MS: 370 (M^+), 338 (M^+ – MeOH)).

16. *Aminolysis of* **33** *with 2-Aminopyridine. 2,5-Dihydro-4-hydroxy-2-methyl-5,7-diphenyl-*N*-(pyrid-2-yl)pyrazolo[3,4-*e*][1,2]thiazine-3-carboxamide 1,1-Dioxide* (**34**). A mixture of **33** (2.1 g, 5.1 mmol) and 2-aminopyridine (0.96 g, 10.2 mmol) in 160 ml of *o*-xylene was maintained at reflux with stirring, while a fairly vigorous stream of Ar was bubbled through the hot soln. Concurrent with some *o*-xylene, MeOH was distilled off, as the reaction proceeded; the *o*-xylene was replenished periodically. After 6 h, the soln. was allowed to cool to r.t., whereby the product started crystallizing. Further crystallization occurred upon cooling of the soln. to 0° for 15 min. Yellowish crystals of anal. pure **34** (2.0 g, 83%), m.p. 239° (dec.), could be collected by filtration. Recrystallizing once more from acetone/hexane was raising the m.p. to 255° (with no further change of the spectroscopic data). IR: 3442/3410*w*, 3072*w*, 1648*s*, 1606*s*, 1570/1552/1531*s*, 1487*s*, 1376/1356/1336*s*, 1170/1154*s*. ^{1}H-NMR (270 MHz, (D_6)DMSO): clear evidence for 2-substituted pyridine moiety, along with two Ph groups; 3.05 (*s*, 3 H). CI-MS (NH_4^+): 474 ([M + H]$^+$), 410 (474 – SO_2), 354 (474 – PyNCO).

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