78. Tricyclic Pyridine Derivatives with High Affinity to the Central Benzodiazepine Receptor

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Dedicated to Dr. *O. Isler* on the occasion of his 80th birthday

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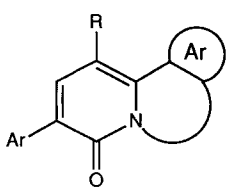
Novel tricyclic heterocycles were prepared and evaluated for their affinity to the central benzodiazepine receptor. The most potent compounds with IC_{50}'s in the nanomolar range were found among thienoquinolizines and benzo[*a*]quinolizines (*cf. Tables 2–5*). The central ring of the tricyclic ring system may be partially unsaturated (*cf. Tables 2* and *4*) or fully unsaturated (*cf. Tables 3* and *5*) without loss of the high affinity to the receptor. The position of the ester group in the pyridinone ring is crucial for good binding (*cf. Tables 1* and *2*). It may be replaced by a broad variety of functional groups, *e.g.* amides, alkyl carbamates, alkyl groups, and hydroxyalkyl groups (*cf. Tables 2–5*). In the benzo[*a*]quinolizines, shifting the halogen atom from C(10) to C(9) leads to complete loss of affinity to the benzodiazepine receptor (*cf. Table 4*).

1. Introduction. – About thirty years after the launch of chlorodiazepoxide and diazepam, benzodiazepine receptor ligands continue to be the most important drugs for the treatment of various forms of anxiety, sleep disorders, certain types of epilepsies and for the use in anesthesiology. They exert their pharmacological effects by interacting with the benzodiazepine receptor, a modulatory drug-binding site of the $GABA_A$ receptor [1]. The identification of benzodiazepine receptors in the central nervous system [2] [3] and the establishment of an *in vitro* receptor binding assay challenged the search for new ligands differing structurally from the benzodiazepines.

A synthetic program was initiated by our group aiming at the preparation of new tricyclic benzodiazepine receptor ligands of general formula **a** containing as common structural element a pyridinone ring. Syntheses and structure-affinity relationships of these novel benzodiazepine receptor ligands are discussed[2]).



a

Ar: aromatic or heteroaromatic ring

R : ester, carboxamide, hydroxyalkyl, alkylcarbamates, alkyl

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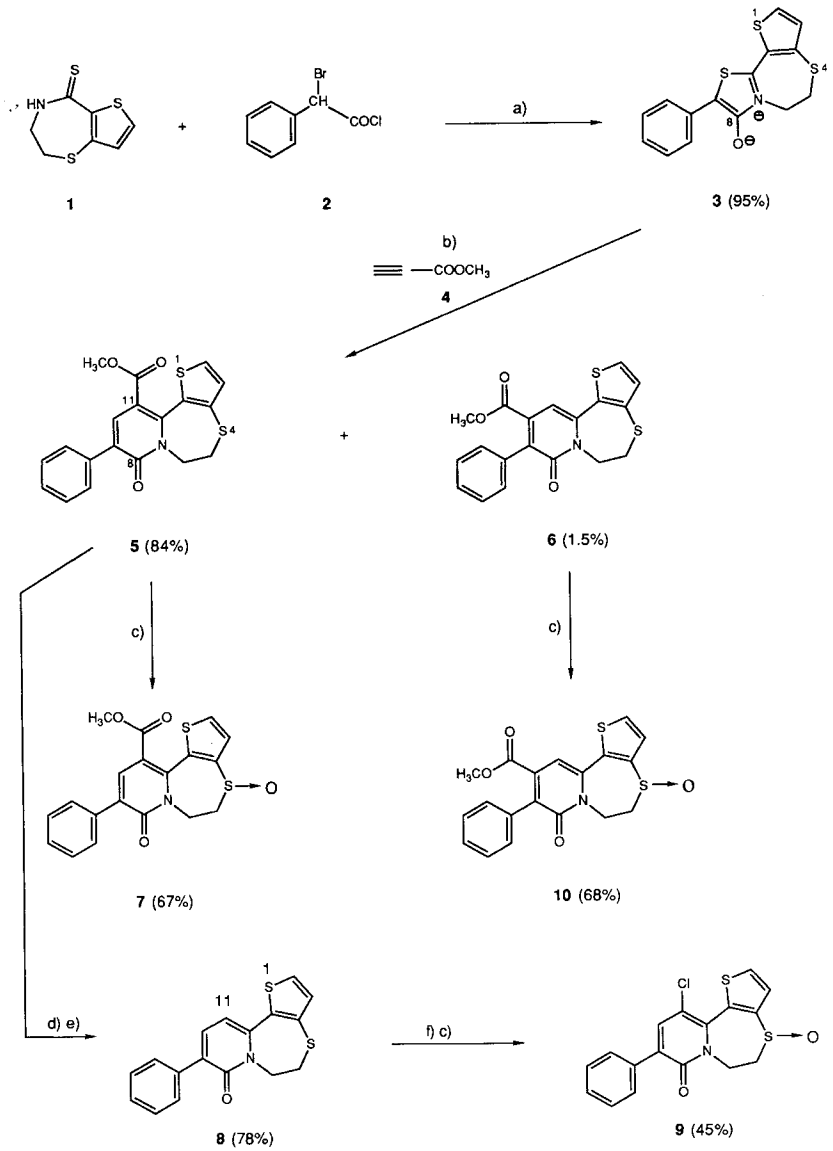
[2]) Detailed pharmacological profiles of selected compounds will be published elsewhere.

2. Results. – 2.1. *Preparation of 5,6-Dihydro-9-phenyl-8*H*-pyrido[1,2-*d*]thieno-[2,3-*f*][1,4]thiazepin-8-ones* (*Scheme 1*). Reaction of thiolactam **1** with (bromo)-(phenyl)acetyl chlorid (**2**) followed by treatment with Et_3N yielded mesoionic thiazole derivative **3** (*Scheme 1*). This compound underwent 1,3-dipolar cycloaddition [4] at 80–110° with methyl prop-2-ynoate (**4**) to give, after extrusion of sulfur from the primary

Scheme 1

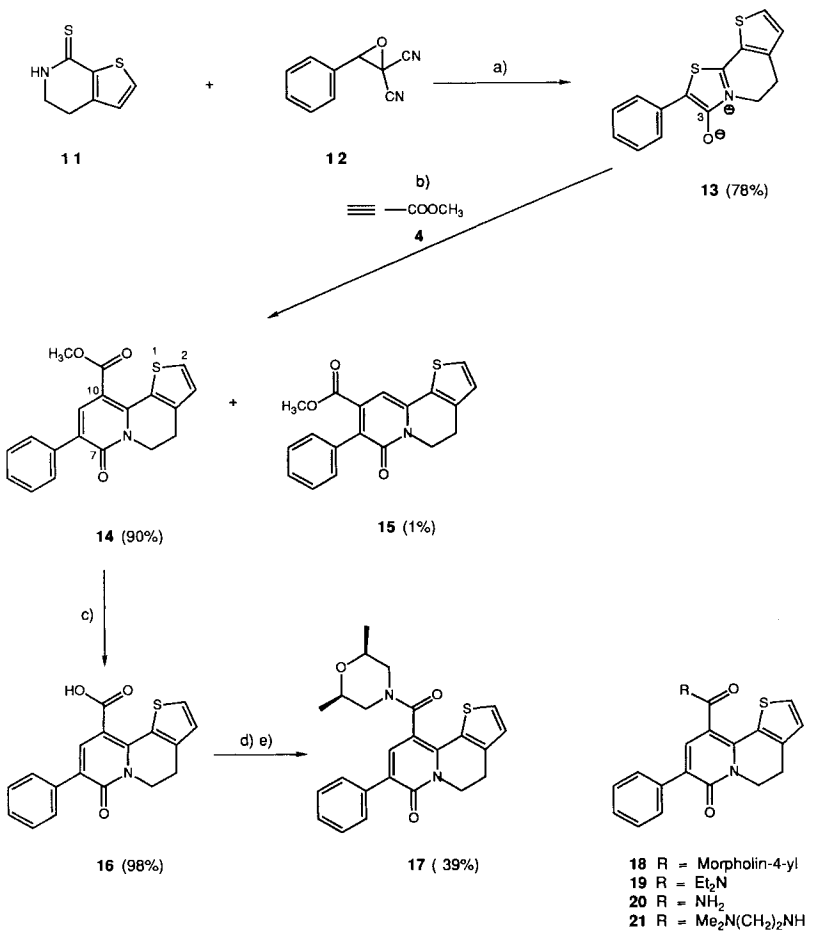


a) R.t., CH_2Cl_2, followed by 1.1 mol-equiv. of Et_3N. b) Toluene, reflux. c) 1 mol-equiv. of 3-$ClC_6H_4CO_3H$, 0°, CH_2Cl_2. d) NaOH, H_2O/MeOH. e) 260–280°/0.5 Torr. f) *N*-Chlorosuccinimide, 20–25°, CCl_4.

adduct under the reaction conditions, a mixture of regioisomeric pyridinones **5** and **6**. In accordance with [4], **5** was the main product. Oxidation of **5** and **6** under carefully controlled conditions furnished sulfoxides **7** and **10**, respectively. Furthermore, **5** was hydrolyzed and the resulting acid decarboxylated to pyridinone derivative **8** in excellent overall yield. Chlorination of **8** occurred selectively at C(11). Subsequent oxidation with 3-chloroperbenzoic acid provided sulfoxide **9**.

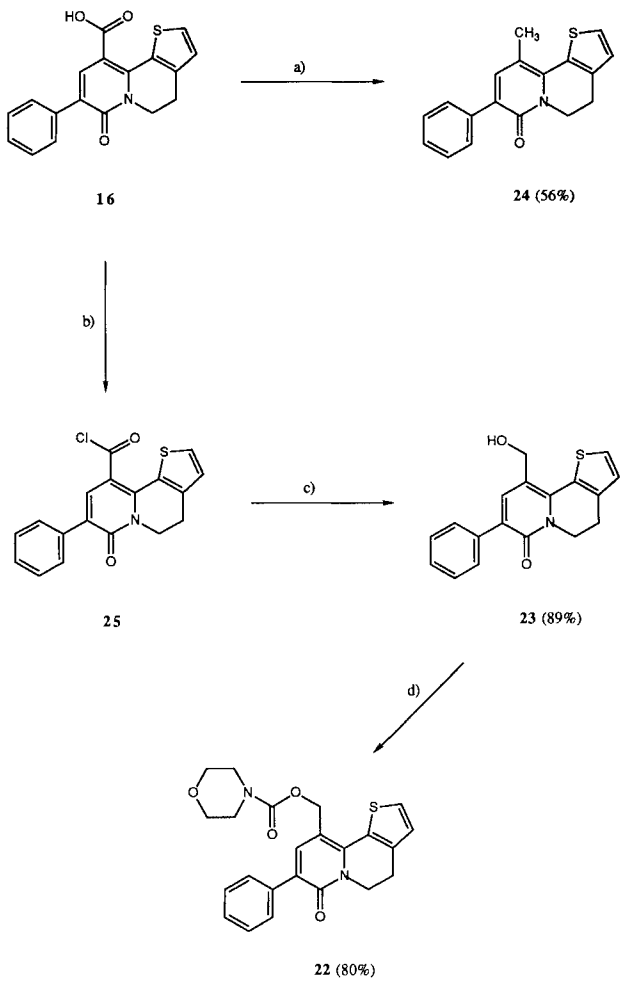
2.2. *Preparation of Thienoquinolizinones.* 2.2.1. *4,5-Dihydro-8-phenyl-7*H*-thieno-[2,3-a]quinolizin-7-ones* (*Scheme 2*). Using the same methodology as described in *Sect. 2.1*, thiolactam **11** [5] was reacted with **12** [6] to give mesoionic thiazole **13** in good yield (*Scheme 2*). Then, 1,3-dipolar cycloaddition with **4** furnished the regioisomeric pyridinones **14** and **15** which could be easily separated by chromatography on a silica-gel

Scheme 2



a) DMF, 2 h, r.t. b) Toluene, reflux. c) NaOH, MeOH/H_2O, reflux. d) $SOCl_2$. e) *cis*-2,6-Dimethylmorpholine.

Scheme 3



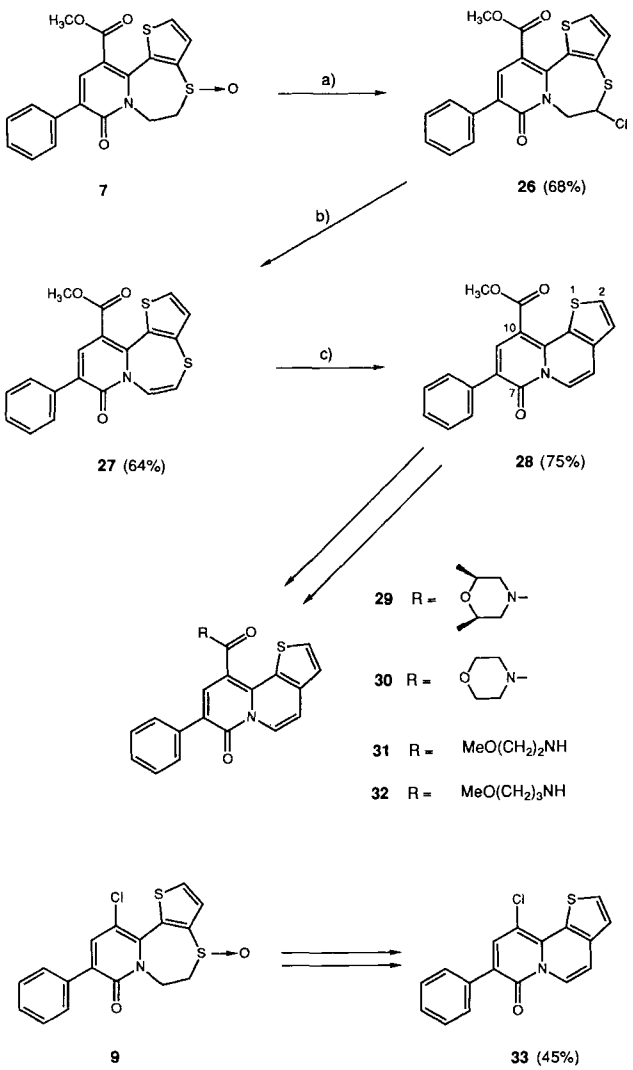
a) $BH_3 \cdot S(CH_3)_2$, THF, −15° to 65°. b) $SOCl_2$. c) $NaBH_4$, THF/DMF, r.t. d) PhOCOCl, pyridine, dioxane, r.t., followed by excess morpholine.

column. Saponification of **14** in boiling aqueous methanolic NaOH gave acid **16** which was transformed *via* its acyl chloride to amide **17**. Amides **18**–**21** were prepared similarly.

Dihydro-thienoquinolizines **23** and **24** were obtained from **16** by reduction of the corresponding acyl chloride **25** with $NaBH_4$ and by treatment with $BH_3 \cdot Me_2S$ in THF, respectively (*cf. Scheme 3*). Subsequently, alcohol **23** was transformed to carbamate **22** (*cf. Table 2*).

2.2.2. *8-Phenyl-7*H*-thieno[2,3-*a*]quinolizin-7-ones* (*Schemes 4* and *5*). The synthesis of unsaturated thienoquinolizine derivatives was achieved by two different synthetic pathways. Since many examples of ring contractions of thiazepines to pyridines are

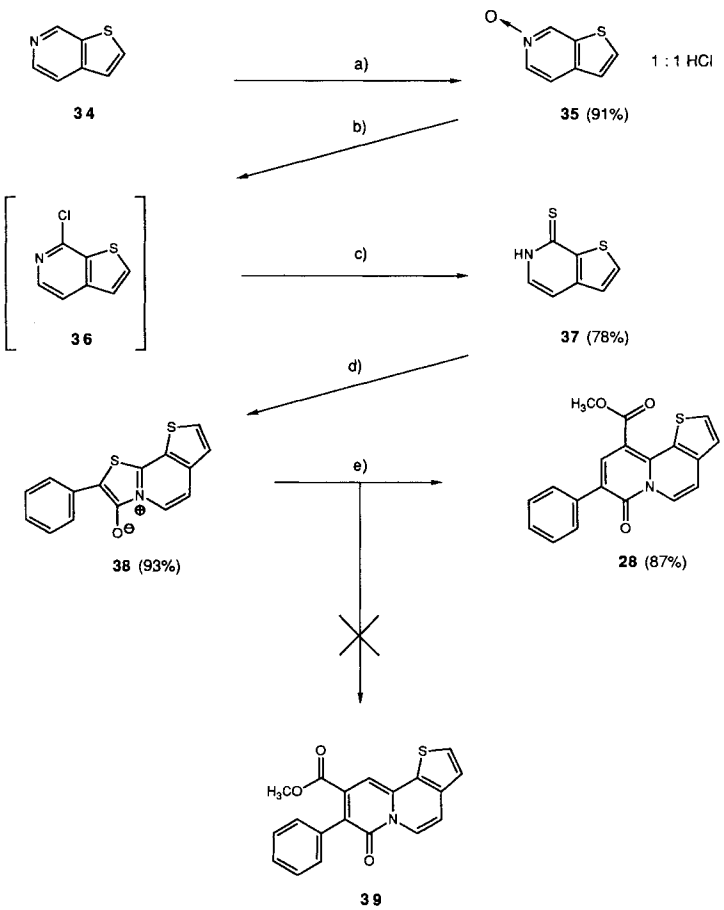
Scheme 4



a) $SOCl_2$, r. t. b) DBN, DMSO, 70–75°. c) Xylene, reflux, 24 h.

described in the literature [7], a first synthetic strategy made use of the available thienothiazepines described in *Sect. 2.1.* Thus, sulfoxide **7** was treated with $SOCl_2$ and the resulting α-chloro thioether **26** was heated in DMSO in the presence of DBN (1,5-diazabicyclo[4.3.0]non-5-ene) to eliminate HCl (*Scheme 4*). Prolonged heating of unsaturated thiazepine derivative **27** in xylene furnished the target intermediate **28** in good yield which, by classical methodology, gave carboxamides **29–32.** Analogously and in comparable yield, chlorinated derivative **33** was obtained from **9.**

Scheme 5

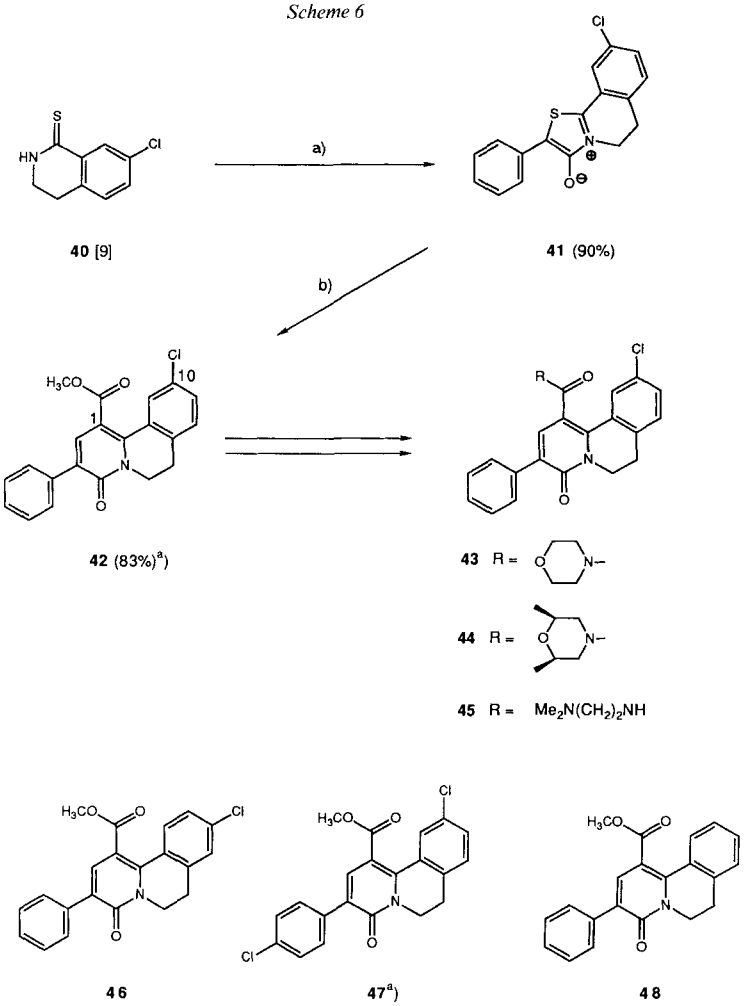


a) 1 mol-equiv. of $3\text{-}ClC_6H_4CO_3H$, CH_2Cl_2, −5°, followed by sat. HCl in Et_2O. b) $POCl_3$, dioxane, 88–93°. c) $NaHS \cdot H_2O$, DMF, 110–115°. d) PhCHBrCOCl (**2**), CH_2Cl_2, r.t., followed by 2.25 mol-equiv. of Et_3N. e) 2 mol-equiv. of $CH{\equiv}CCOOCH_3$ (**4**), toluene, reflux.

Subsequently, a more straightforward synthesis for ester **28** was developed (*cf. Scheme 5*). Thieno[2,3-*c*]pyridine (**34**) [8] was transformed to its *N*-oxide **35** by treatment with 3-chloroperbenzoic acid. Rearrangement of **35** to the 7-chloro derivative **36** was achieved by treatment with $POCl_3$. Compound **36** was not purified but immediately reacted with NaHS to give thiolactam **37** from which ester **28** was prepared according to described methodology. The cycloaddition step **38**→**28** proceeded in a completely regioselective manner, no trace of the regioisomer **39** could be detected by TLC.

2.3. *Preparation of Benzo[*a*]quinolizinones.* 2.3.1. *3-Aryl-6,7-dihydro-4*H*-benzo[*a*]quinolizin-4-ones* (*Scheme 6*). The preparation of esters **42** (from **40** *via* **41**), **46**, **47**, and **48** was accomplished *via* the synthetic pathway described in *Sect. 2.1* and *2.2*. By known methods, carboxamides **43**–**45** were prepared (*cf. Exper. Part*).

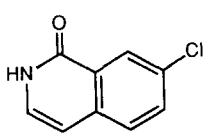
Scheme 6



a) PhCHBrCOCl (**2**), DMF, followed by 2 mol-equiv. of Et_3N. b) $CH{\equiv}CCOOCH_3$ (**4**), toluene, reflux.

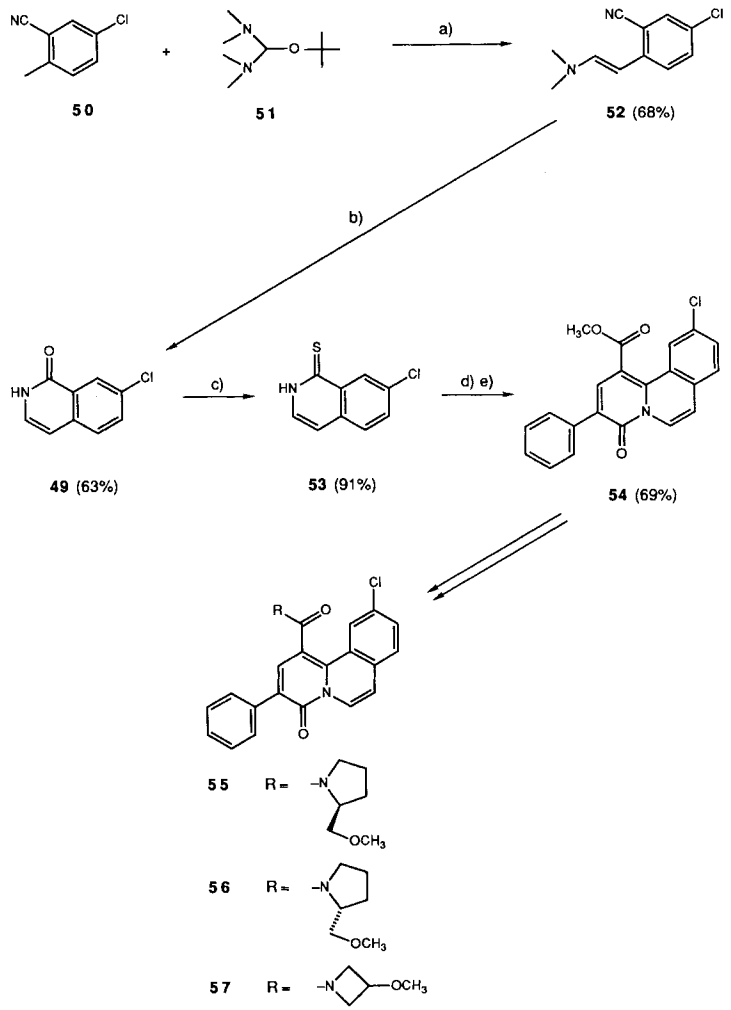
[a]) In addition, 2% of the regioisomeric ester bearing the ester group at C(2) was isolated (*cf. Exper. Part*).

2.3.2. *3-Phenyl-4*H-*benzo[a]quinolizin-4-ones* (*Scheme 7*). Since we intended to apply the same synthetic strategy used successfully for the preparation of the compounds listed in *Scheme 6* to unsaturated analogues, a more convenient and safe preparation than the one known from literature [10] for the starting lactam **49** was required. Thus, benzonitrile



49

Scheme 7



a) 1.2 mol-equiv. of **51**, 122–130°. b) Conc. HCl/EtOH, reflux. c) P_2S_5, pyridine, reflux. d) PhCHBrCOCl (**2**), CH_2Cl_2, r.t., followed by 2.25 mol-equiv. of Et_3N. e) 2 mol-equiv. of $CH{\equiv}CCOOCH_3$ (**4**), 1,2-dichloroethane, reflux.

derivative **50** was treated with DMF-derived aminal **51** to give (*E*)-configurated enamine **52** which was purified by crystallization (*Scheme 7*). When **52** was heated in ethanolic HCl, **49** was obtained in 63% yield. The remainder of the synthesis was straightforward, furnishing ester **54** *via* **53** in 69% overall yield. From **54**, carboxamides **55–57** were prepared.

3. Discussion: Structure Affinity Relationship. – The key step for the preparation of these new benzodiazepine receptor ligands is the 1,3-dipolar cycloaddition of mesoionic thiazoles **b** with acetylenic dipolarophile **4** affording, with high regioselectivity, pyridinone

derivatives **a** in good yield (*Scheme 8*). Regioisomers **c** are isolated only in minute amounts (0–2% yield) as expected from similar cycloadditions described by *Potts* and coworkers [4].

Scheme 8

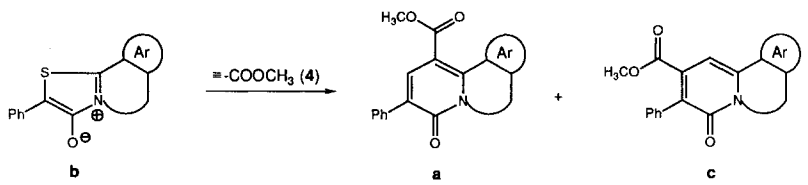
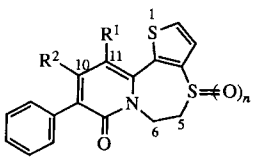


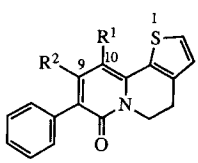
Table 1. *Affinity of Thiazepine Derivatives to the Benzodiazepine Receptor* [2] [3] (*cf. Scheme 1*)

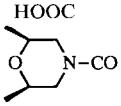
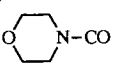
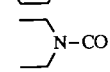
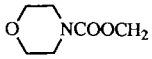


Compound	R^1	R^2	n	IC_{50} [nM]
5	MeOCO	H	0	140
7	MeOCO	H	1	27
10	H	MeOCO	1	inact.
9	Cl	H	1	30
27 (see *Scheme 3*)[a])	MeOCO	H	0	110

[a]) Double bond between C(5) and C(6).

Table 2. *Affinity of Dihydro-thienoquinolizinones to the Benzodiazepine Receptor* [2] [3] (*cf. Scheme 2*)



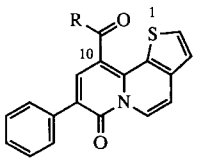
Compound	R^1	R^2	IC_{50} [nM]
14	MeOCO	H	2.5
15	H	MeOCO	> 1000
16	HOOC	H	> 1000
17		H	18
18		H	10
19		H	6.4
20	H_2N–CO	H	140
21	$Me_2N(CH_2)_2NHCO$	H	19
22		H	0.9
23	$HOCH_2$	H	50
24	Me	H	28

The affinity to the benzodiazepine receptor of the compounds prepared was determined in the [^{3}H]diazepam binding assay [2] [3]. As seen from *Tables 1* and *2*, only the main cycloaddition products **a** are potent ligands to the receptor, whereas the regioisomers **c** (*Table 1:* **10**; *Table 2:* **15**) proved to be inactive[3]).

Generally, the thiazepine derivatives are less active than the quinolizine derivatives. The most active compounds, sulfoxides **7** and **9**, show an IC_{50} of *ca.* 30 nM, while in the quinolizine series, compounds with IC_{50}'s below 10 nM are found. Introduction of a double bond into the central ring leading to a planar ring system does not influence the affinity to the receptor (*cf. Tables 2* and *3*: **14** and **28**, **17** and **29**, **18** and **30**; *Tables 4* and *5*: **42** and **54**).

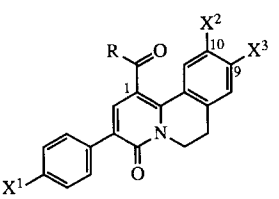
In the quinolizine series, the annelated thiophene ring may be replaced by a suitably substituted benzene ring. With an unsubstituted benzene ring, the affinity drops signifi-

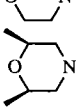
Table 3. *Affinity of Thienoquinolizinones to the Benzodiazepine Receptor* [2] [3] (*cf. Scheme 3*)



Compound	R	IC_{50} [nM]
28	MeO	3
29		17
30		4.3
31	$MeO(CH_2)_2NH$	1.5
32	$MeO(CH_2)_3NH$	7.2

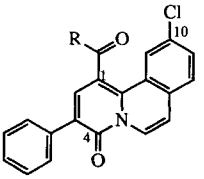
Table 4. *Affinity of Dihydro-benzo[a]quinolizines to the benzodiazepine Receptor* [2] [3] (*cf. Scheme 5*)

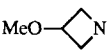


Compound	R	X^1	X^2	X^3	IC_{50} [nM]
42	MeO	H	Cl	H	3.5
46	MeO	H	H	Cl	> 1000
47	MeO	Cl	Cl	H	390
48	MeO	H	H	H	45
43		H	Cl	H	3.8
44		H	Cl	H	13
45	$Me_2N(CH_2)_2NH$	H	Cl	H	3.7

[3]) The same is true for the regioisomeric esters of **42** and **47** (*cf. Scheme 6*).

Table 5. *Affinity of Benzo[a]quinolizinones to the Benzodiazepine Receptor* [2] [3] (*cf. Scheme 6*)



Compound	R	IC_{50} [nM]
54	MeO	8.0
55		2.6
56		3.9
57		0.9

cantly as demonstrated by comparison of **14** with **48** (*cf. Tables 2* and *4*). On the other hand, replacement of the thiophene ring by a chlorobenzene moiety with the Cl-atom bound to C(10) produces equally active ligands (*cf. Tables 2* and *4*: **14** and **42**, **18** and **43**, **21** and **45**; *Tables 3* and *5*: **28** and **54**). In contrast to this successful variation, compounds bearing a Cl-atom at C(9) are inactive (*cf. Table 4*: **46**). Likewise, introduction of a Cl-atom to the *para*-position of the phenyl group at C(3) leads to a significant decrease of affinity by a factor of about hundred, compared to the unsubstituted phenyl group (*cf. Table 4*: **42** and **47**)[4]). Finally, the ester group may be replaced by a variety of other functional groups (*cf. Tables 1–5*). Alcohol **23** and methyl derivative **24** are still rather potent ligands to the receptor. Carbamate **22** represents the most potent ligand identified (IC_{50} = 0.9 nM, *cf. Table 2*).

Thus, this novel series of compounds shows comparable affinity to the benzodiazepine receptor as 1,4-benzodiazepines.

4. Conclusion. – Efficient preparations of novel tricyclic pyridine derivatives are described. These new series of compounds show high affinity to the central benzodiazepine receptor[5]). Qualitative structure-affinity relationships are deduced which obey relatively strict rules with regard to structural changes.

We wish to thank Ms. *M.-E. Bixel* for the results of the [^{3}H]diazepam binding assay and our colleagues from the Central Research Department for physical and analytical data: Dr. *W. Arnold* (NMR), Mr. *A. Bubendorf* (IR), Dr. *A. Dirscherl*† (microanalyses), Dr. *G. Englert* (NMR), Dr. *M. Grosjean* (UV, opt. rotation), Mr. *W. Meister* (MS), and Dr. *W. Vetter* (MS). We are grateful to Mrs. *A. Perrin* for her efficient typewriting of this manuscript.

[4]) This observation fits also for any substituent in *meta*- or *ortho*-position of the phenyl ring (results not shown).

[5]) Within the thieno- and benzo[*a*]quinolizines, compounds acting as full or partial agonists at the benzodiazepine receptor were identified. Detailed pharmacological profiles of interesting compounds, *i.e.* partial agonists, will be published elsewhere.

Experimental Part

(The authors wish to thank Mrs. *V. Bitsch*, Ms. *S. Herzig*, Mr. *S. Burner*, Mr. *R. Canesso*, and Mr. *R. Simon* for their skillful technical assistance)

General. Column chromatography: silica gel *Merck 60* (particle size 0.04–0.063 mm) unless stated differently. TLC: 0.25 mm precoated silica gel plates (*Merck*, silica gel *60 F_{254}*). M.p.: *Büchi-510* apparatus; uncorrected. UV: in EtOH; λ in nm (log ε). IR spectra: in KBr unless stated differently; in cm^{-1}. ^{1}H-NMR: in $CDCl_3$ unless stated differently; chemical shifts in ppm relative to TMS (= 0 ppm), coupling constants J in Hz. MS: m/z (% rel. abundance). Correct elemental analyses were obtained for all compounds: C, H, N, S, Cl ± 0.30%.

1. *Thieno[2,3-c]pyridine-7(6H)-thione* (**37**). 1.1. *Thieno[2,3-c]pyridine 6-Oxide Hydrochloride* (**35**·HCl). Thieno[2,3-*c*]pyridine (338 g, 2,5 mol; **34**) was dissolved in CH_2Cl_2 (6.25 l) and cooled to −5° to 0°. A soln. of 3-$ClC_6H_4CO_3H$ (507.5 g, 2.5 mol; purity 85%) in CH_2Cl_2 (6.25 l) was added dropwise within 2 h. Sat. etheral HCl (1.0 l) was added within 1 h. Pale yellow crystals separated from the mixture. After addition of Et_2O (1.5 l), the crystals were filtered off and washed with Et_2O (1.5 l): **35**·HCl (427.3 g, 91%). White crystals. M.p. 201–205° (dec.). Recrystallization from EtOH furnished anal. pure **35**·HCl. M.p. 196–200°. UV: 300 (4.18), 272 (3.65), 257 (4.11), 246 (3.99), 236 (4.23), 215 (3.78). IR: 2347*m*, 2225*s*, 2046*s*, 1623*m*, 1603*m*, 1550*m*, 1506*m*, 1481*m*, 824*s*. ^{1}H-NMR (60 MHz, DMSO): 7.80 (*dm*, J = 5.0, H–C(3)); 8.25 (*d*, J = 6.5, H–C(4)); 8.60 (*d*, J = 5.0, H–C(2)); 8.75 (*dd*, J = 6.5, 1.5, H–C(5)); 9.90 (*m*, H–C(7)); 12.90 (br., OH). MS: 151 (100, M^+), 135 (67), 96 (46).

1.2. *7-Chlorothieno[2,3-c]pyridine* (**36**). Under Ar, a soln. of **35** (671.4 g, 3.6 mol) in dioxane (4.0 l) was treated with $POCl_3$ (0.66 l, 7.2 mol) and heated to 88° (→exothermic reaction). The oil bath was removed, and the hot soln. was stirred for 10 min and then heated to reflux for 10 min. After evaporation of the solvents, the residue was partitioned between toluene (2 l) and ice-cold H_2O (3 l). The aq. layer was cautiously brought to pH 7 by slow addition of solid Na_2CO_3. The org. layer was separated and the aq. layer again extracted with toluene. The combined org. layers were dried (Na_2SO_4) and evaporated: **36** as a brown oil (581 g).

1.3. *Thieno[2,3-c]pyridine-7(6H)-thione* (**37**). To a soln. of **36** (581 g, *ca.* 3.4 mol) in DMF (1.8 l), NaHS·H_2O (518 g, 7 mol) was added. The mixture was heated to 110–115° for 2 h, more NaHS·H_2O (51.8 g, 0.7 mol) added, and the green mixture heated for another h. After cooling to r.t., the mixture was poured into ice/H_2O (1 l) and brought to pH 4 by dropwise addition of conc. HCl soln. The yellow crystals were filtered off, suspended in H_2O (5 l), and stirred for 30 min. A first crop of raw **37** (475 g) was obtained. The aq. layer was extracted with AcOEt (2 l) yielding *ca.* 50 g of impure material which was suspended together with the first crop in hexane (2.4 l)/Et_2O(0.2 l) and stirred for 1 h at r.t. The crystals were filtered off to give **37** (467.4 g, 78%). M.p. 170–177°. An anal. pure sample of **37** was obtained by recrystallization from toluene/AcOEt/acetone 4:3:1. M.p. 187–189°. IR: 3302*m*, 3164*m*, 1603*s*, 1563*s*. ^{1}H-NMR (80 MHz, DMSO): 7.29 (*d*, J = 6.5, H–C(4)); 7.43 (*d*, J = 5.5, H–C(3)); 7.65 (*d*, J = 6.5, H–C(5)); 8.17 (*d*, J = 5.5, H–C(2)); 13.35 (br., NH). MS: 167 (100, M^+), 140 (44), 134 (32), 122 (13), 70 (19).

2. *7-Chloroisoquinoline-1(2H)-thione* (**53**). 2.1. *5-Chloro-2-[(E)-2-(dimethylamino)vinyl]benzonitrile* (**52**). A mixture of 5-chloro-2-methylbenzonitrile (**50**; 279 g, 1.84 mol) and 1-(1,1-dimethylethoxy)-*N,N,N',N'*-tetramethyl-methanediamine (**51**; 455 ml, 2.2 mol) was heated under Ar to 122–130° (oil-bath temp.). Within the next 2 h *t*-BuOH (195 g) distilled off. The mixture was heated for further 15 min, cooled to r.t., treated with hexane (1.2 l), and then cooled to −20° for 18 h under stirring. The orange crystals were collected by filtration and washed with hexane (300 ml, cooled to 0°): **52** as brown crystals (257.2 g, 67.7%). M.p. 78–80°. An anal. pure sample of **52** was obtained by recrystallization from hexane. M.p. 82–83°. IR: 2215*m*, 1629*s*, 1588*m*, 967*w*. ^{1}H-NMR (250 MHz): 2.91 (*s*, $(CH_3)_2N$); 5.32 (*d*, J = 13.5, ArC*H* = CHN); 6.97 (*d*, J = 13.5, ArCH = C*H*N); 7.26 (*m*, H–C(3), H–C(4)); 7.40 (*m*, H–C(6)). MS: 206 (24, M^+), 205 (100), 191 (22), 169 (15).

2.2. *7-Chloroisoquinolin-1(2H)-one* (**49**). At 0–5°, **52** (257.2 g, 1.24 mol) was suspended in EtOH (1.25 l) under Ar. To the stirred suspension, conc. HCl soln. (0.5 l) was added dropwise. The temp. was raised to 5–11° and conc. HCl soln. (0.75 l) slowly added. Then, the soln. was heated in an oil bath (120–122°). Some undissolved material was removed by filtration of the hot soln. The clear filtrate was treated with H_2O (6.0 l) and stirred overnight. The pale yellow crystals were isolated by filtration and washed 3 times with H_2O (400 ml). The raw material was suspended in *tert*-butyl methyl ether and stirred for 30 min. The crystals were filtered off and washed with *tert*-butyl methyl ether: **49** (141.5 g, 63%) as beige crystals. M.p. 240–244°. Recrystallization from MeOH furnished an anal. pure sample. M.p. 245–247°. IR: 3160*m*, 1660*s*, 1634*s*, 1603*m*, 1542*m*, 1475*m*, 834*s*. ^{1}H-NMR (250 MHz, DMSO): 6.58 (*d*, J = 7.8, H–C(4)); 7.22 (*dd*, J = 7.8, 6.5, H–C(3)); 7.61–7.82 (*m*, H–C(5), H–C(6)); 8.12 (*d*, J = 1.0, H–C(8)); 11.45 (br., NH). MS: 179 (100, M^+), 152 (30), 144 (22), 89 (30).

2.3. *7-Chloroisoquinoline-1(2H)-thione* (**53**). Under Ar, **49** (156.4 g, 0.87 mol) and P_2S_5 (213 g, 0.96 mol) were heated to reflux in pyridine (870 ml) for 90 min. The mixture was cooled in an ice-bath, and H_2O (2.5 l) was added

slowly. Yellow crystals precipitated. The suspension was stirred overnight and **53** isolated by filtration (155.5 g, 91%). M.p. 276° (dec.). Recrystallization from MeCN afforded anal. pure material. M.p. 273° (dec.). IR: 3139*m*, 1624*s*, 1567*s*, 1499*m*, 826*m*. ^{1}H-NMR (250 MHz, DMSO): 7.16 (*d*, J = 6.8, H–C(4)); 7.45 (*t*-like *m*, H–C(3)); 7.70–7.88 (*m*, H–C(5), H–C(6)); 8.73 (*m*, H–C(8)); 13.50 (br., NH). MS: 195 (100, M^+), 168 (24), 162 (24).

Similarly were prepared:

2.4. *2,3-Dihydrothieno[2,3-f][1,4]thiazepine-5(4H)-thione* [11] (**1**) in 86% yield as yellow crystals. M.p. 138–139° (AcOEt). UV: 348 (4.03), 308 (3.66), 287 (3.89), 258 (3.36), 217 (sh, 4.02). IR: 3188*m*, 1550*m*, 1495*m*, 824*w*. ^{1}H-NMR (90 MHz): 3.00–3.32 (*m*, 2 H–C(2)); 3.37–3.80 (*m*, 2 H–C(3)); 6.64 (*d*, J = 5.2, H–C(8)); 7.28 (*d*, J = 5.2, H–C(7)); 9.25 (br., NH). MS: 201 (100, M^+), 186 (24), 96 (29).

2.5. *6-Chloro-3,4-dihydroisoquinoline-1(2H)-thione*. From 1-chloro-3-(2-isocyanatoethyl)benzene according to [9] in 32% overall yield. M.p. 127–129° (AcOEt). IR: 3450*w*, 1600*s*, 1572*s*, 1532*s*, 1343*m*, 1208*s*, 1086*m*, 1012*m*, 850*m*, 828*m*. ^{1}H-NMR (60 MHz, DMSO): 2.92 (*t*, J = 6.5, 2 H–C(4)); 3.46 (*m*, 2 H–C(3)); 7.27–7.50 (*m*, H–C(5), H–C(7)); 8.31 (*d*, J = 9, H–C(8)); 10.44 (br., NH). MS: 197 (100, M^+), 168 (80), 162 (35), 133 (20), 89 (20).

3. *Mesoionic Thiazole Derivatives*. 3.1. *2-Phenylthiazolo[3,2-a]thieno[2,3-c]pyridin-4-ium 3-Oxide* (**38**). Under Ar, **37** (250.9 g, 1.5 mol) was suspended in CH_2Cl_2 (15 l) and treated dropwise with **2** (381.7 g, 1.5 mol; purity *ca.* 90%). After stirring for 45 min, Et_3N (0.47 l, 3.4 mol) was added. The violet soln. was washed 3 times with H_2O (5.0 l). The H_2O layers were extracted with CH_2Cl_2 (4.0 l). The combined org. layers were evaporated and the residue treated with toluene (2.0 l) and again evaporated. The red crystals were suspended in Et_2O (2.0 l) and the product isolated by filtration. After washing with Et_2O, **38** was obtained as red-brown crystals (395.7 g, 93%). M.p. 192–201° (dec.). Recrystallization from $CHCl_3$/Et_2O/hexane 1:1:1 afforded an anal. pure sample of **38** M.p. 195–200°. UV: 462 (4.23), 346 (4.05), 300 (4.03), 287 (4.00), 276 (4.18), 262 (4.08), 238 (4.42), 222 (4.20). IR: 1621*s*, 1586*m*, 1517*w*, 1490*m*, 825*m*, 753*m*. ^{1}H-NMR (80 MHz): 7.46–7.51 (*m*, 3 arom. H); 7.47 (*d*, J = 5.5, H–C(7)); 7.68 (*d*, J = 7.5, H–C(6)); 7.81 (*d*, J = 5.5, H–C(8)); 7.88–8.13 (*m*, 2 arom. H); 8.88 (*d*, J = 7.5, H–C(5)). MS: 283 (100, M^+), 254 (50), 121 (100), 77 (25).

Similarly were prepared:

3.2. *5,6-Dihydro-9-phenylthiazolo[3,2-d]thieno[2,3-f][1,4]thiazepin-7-ium 8-Oxide* (**3**). From **1** and **2** in 95% yield. M.p. 196–198° ($CHCl_3$/Et_2O). UV: 493 (4.22), 388 (2.86), 356 (3.68), 330 (3.59), 282 (4.15), 245 (3.78), 221 (sh, 4.08). IR: 1622*s*, 1587*m*, 1493*m*, 1410*m*, 1140*m*, 751*m*. ^{1}H-NMR (60 MHz): 3.32–3.56 (*m*, 2 H–C(5)); 4.63–4.88 (*m*, 2 H–C(6)); 6.88 (*d*, J = 5.5, H–C(3)); 7.02–7.53 (*m*, 3 arom. H); 7.37 (*d*, J = 5.5, H–C(2)); 7.75–8.02 (*m*, 2 arom. H). MS: 317 (100, M^+), 201 (10), 168 (60), 141 (28), 121 (24).

3.3. *9-Chloro-5,6-dihydro-2-phenylthiazolo[2,3-a]isoquinolin-4-ium 3-Oxide* (**41**). From **40** [9] and **2** in 90% yield. M.p. 260–262° (dec., DMF/AcOEt). IR: 1620*s*, 1590*s*, 1500*m*, 1488*m*, 1137*m*, 753*m*. ^{1}H-NMR (270 MHz): 3.16 (*t*, J = 7.5, 2 H–C(6)); 4.30 (*t*, J = 7.5, 2 H–C(5)); 7.16 (*dd*, J = 7.5, 2.0, H–C(8)); 7.26 (*d*, J = 7.5, H–C(7)); 7.32–7.38 (*m*, 3 arom. H); 7.53 (*d*, J = 2.0, H–C(10)); 7.97 (*dm*, J = 7.5, 2 arom. H). MS: 313 (100, M^+), 121 (50).

3.4. *9-Chloro-2-phenylthiazolo[2,3-a]isoquinolin-4-ium 3-Oxide*. From **53** and **2** in 85% yield. M.p. 251–252° (dec.; $CHCl_3$/Et_2O). UV: 486 (4.19), 336 (3.26), 329 (3.88), 321 (3.78), 316 (3.81), 307 (3.75) 283 (4.33), 277 (4.25), 272 (4.33), 258 (4.16), 225 (4.56), 208 (4.34). IR: 1644*s*, 1603*s*, 1495*m*, 835*m*, 751*m*. ^{1}H-NMR (250 MHz): 7.35–7.43 (*m*, 3 arom. H); 7.51 (*d*, J = 7.3, H–C(6)); 7.64 (*dd*, J = 8.7, 2.0, H–C(8)); 7.79 (*d*, J = 8.7, H–C(7)); 7.94–8.05 (*m*, 2 arom. H); 8.12 (*d*, J = 2.0, H–C(10)); 8.71 (*d*, J = 7.3, H–C(5)). MS: 311 (71, M^+), 282 (14), 248 (12), 121 (100), 77 (18).

3.5. *5,6-Dihydro-2-phenylthiazolo[2,3-a]isoquinolin-4-ium 3-Oxide*. From 3,4-dihydroisoquinoline-1(2*H*)-thione [12] and **2** in 50% yield. M.p. 208–210° (MeCN/dioxane). IR: 1625*s*, 1588*s*, 1500*s*, 1135*s*, 752*s*, 686*m*. ^{1}H-NMR (60 MHz): 3.12 (*t*, J = 7.0, 2 H–C(6)); 4.25 (*t*, J = 7.0, 2 H–C(5)); 7.03–7.63 (*m*, 7 arom. H); 7.77–8.07 (*m*, 2 arom. H). MS: 279 (100, M^+), 121 (22).

3.6. *8-Chloro-5,6-dihydro-2-phenylthiazolo[2,3-a]isoquinolin-4-ium 3-Oxide*. From 6-chloro-3,4-dihydroisoquinoline-1(2*H*)-thione [9] and **2** in 49% yield. M.p. 253–254° (dec.; dioxane). IR: 1610*s*, 1590*s*, 1495*s*, 1482*m*, 1137*m*, 752*s*. ^{1}H-NMR (90 MHz): 3.15 (*t*, J = 7.5, 2 H–C(6)); 4.25 (*t*, J = 7.5, 2 H–C(5)); 7.0–7.5 (*m*, 6 arom. H); 7.85–8.05 (*m*, 2 arom. H). MS: 313 (100, M^+), 121 (63).

3.7. *5,6-Dihydro-2-phenylthiazolo[3,2-a]thieno[2,3-c]pyridin-4-ium 3-Oxide* (**13**). To a soln. of 4,5-dihydrothieno[2,3-*c*]pyridine-7(6*H*)-thione (**11**; 101.4 g, 0.6 mol) in DMF (600 ml) under Ar, 3-phenyloxirane-2,2-dicarbonitrile (**12**; 122.5 g, 0.72 mol) [13] was added with stirring. After *ca.* 15 min, the product began to crystallize from the dark red. soln. After 2 h, the dark red crystals of **13** were filtered off, washed with AcOEt, and dried at 75°/0.1 Torr. Evaporation of the mother liquor to about half of its volume and trituration with AcOEt gave another crop of **13** (total yield: 133.2 g, 78%) which was sufficiently pure for the subsequent cycloaddition step. Recrystallization from dioxane/MeCN afforded anal. pure **13**. M.p. 225° (dec.). IR: 1615*s*, 1590*s*, 1500*s*, 1140*m*, 758*m*.

^{1}H-NMR (60 MHz): 3.13 (*t*, *J* = 8.0, 2 H–C(6)); 4.33 (*t*, *J* = 8.0, 2 H–C(5)); 6.98 (*d*, *J* = 5.0, H–C(7)); 7.42 (*d*, *J* = 5.0, H–C(8)); 6.90–7.50 (*m*, 3 arom. H); 7.75–8.05 (*m*, 2 arom. H). MS: 285 (100, M^+), 121 (48).

Similarly was prepared:

3.8. *9-Chloro-2-(4-chlorophenyl)-5,6-dihydrothiazolo[2,3-*a*]isoquinolin-4-ium 3-Oxide.* From thiolactam **40** [9] and 3-(4-chlorophenyl)oxirane-2,2-dicarbonitrile [6] in acetone (28%). M.p. > 276° (dioxane). IR: 1608*s*, 1578*s*, 1485*s*, 1135*m*, 1090*m*, 830*m*, 820*m*. ^{1}H-NMR (80 MHz): 3.12 (*t*, *J* = 7.0, 2 H–C(6)); 4.24 (*t*, *J* = 7.0, 2 H–C(5)); 7.10–7.47 (*m*, 5 arom. H); 7.70–7.90 (*m*, 2 arom. H). MS: 347 (100, M^+), 181 (11), 164 (25), 155 (68).

4. *1,3-Dipolar Cycloaddition of Mesoionic Thiazole Derivatives with Methyl Prop-2-ynoate* (**4**). 4.1. *Methyl 5,6-Dihydro-8-oxo-9-phenyl-8*H*-pyrido[1,2-*d*]thieno[2,3-*f*][1,4]thiazepine-11-carboxylate* (**5**) *and -10-carboxylate* (**6**). Under Ar, **3** (6.34 g, 20 mmol) in toluene (200 ml) in the presence of **4** (2.0 ml, 24 mmol) was heated to reflux temp. for 8 h. The solvent was evaporated and **5**/**6** separated by chromatography (toluene/AcOEt 4:1).

The main product **5** was recrystallized from EtOH yielding pure **5** (6.2 g, 84%). Yellow crystals. M.p. 158–160°. UV: 360 (4.21), 308 (3.83), 292 (3.86), 278 (3.83), 258 (sh, 4.20), 228 (sh, 4.21). IR: 1715*s*, 1650*s*, 1600*w*, 1547*m*, 1497*m*, 1277*m*, 754*w*, 706*m*. ^{1}H-NMR (60 MHz): 3.21–3.58 (br., 2 H–C(5), H–C(6)); 3.68 (*s*, CH_3O); 4.50–5.50 (br., H–C(6)); 7.08 (*d*, *J* = 5.0, H–C(3)); 7.21–7.55 (*m*, 3 arom. H); 7.51 (*d*, *J* = 5.0, H–C(2)); 7.55–8.88 (*m*, 2 arom. H); 8.00 (*s*, H–C(10)). MS: 369 (100, M^+), 336 (69), 310 (90).

By recrystallization from MeOH, **6** was obtained in 1.5% yield. Yellow crystals. M.p. 166–167°. UV: 376 (4.15), 300 (3.68), 279 (3.76), 264 (3.71). IR: 1715*s*, 1650*s*, 1590*s*, 1573*m*, 1540*m*, 1266*m*, 1235*s*, 739*w*, 700*w*. ^{1}H-NMR (60 MHz): 3.35–3.65 (*m*, 2 H–C(5)); 3.64 (*s*, CH_3O); 4.35–4.65 (*m*, 2 H–C(6)); 6.66 (*s*, H–C(11)); 7.15 (*d*, *J* = 5.0, H–C(3)); 7.21–7.62 (*m*, H–C(2), 5 arom. H). MS: 369 (100, M^+), 336 (66), 310 (16).

Similarly were prepared:

4.2. *Methyl 4,5-Dihydro-7-oxo-8-phenyl-7*H*-thieno[2,3-*a*]quinolizine-10-carboxylate* (**14**) *and -9-carboxylate* (**15**). From **13** and **4**.

14: Yield 90%. M.p. 117–118° (AcOEt/(i-Pr)$_2$O). IR: 1720*s*, 1645*s*, 1535*s*, 1510*s*, 1270*s*, 1250*s*, 1200*s*, 1132*s*, 794*m*, 748*m*, 700*m*. ^{1}H-NMR (80 MHz): 3.00 (*t*, *J* = 7.0, 2 H–C(4)); 3.95 (*s*, CH_3O); 4.47 (*t*, *J* = 7.0, 2 H–C(5)); 7.02 (*d*, *J* = 5.5, H–C(3)); 7.34–7.50 (*m*, 3 arom. H); 7.58 (*d*, *J* = 5.5, H–C(2)); 7.75–7.88 (*m*, 2 arom. H); 7.90 (*s*, H–C(9)). MS: 337 (100, M^+), 322 (16), 306 (10), 278 (19).

15: Yield 1%, after recrystallization from EtOH. M.p. 167.5–168°. IR: 1720*s*, 1645*s*, 1588*s*, 1538*s*, 1258*s*, 808*m*, 782*m*, 705*m*. ^{1}H-NMR (80 MHz): 3.03 (*t*, *J* = 7.0, 2 H–C(4)); 3.61 (*s*, CH_3O); 4.45 (*t*, *J* = 7.0, 2 H–C(5)); 6.63 (*s*, H–C(10)); 7.04 (*d*, *J* = 5.0, H–C(3)); 7.44 (br. *s*, 5 arom. H); 7.47 (*d*, *J* = 5.0, H–C(2)). MS: 337 (100, M^+), 278 (12), 249 (14).

4.3. *Methyl 7-Oxo-8-phenyl-7*H*-thieno[2,3-*a*]quinolizine-10-carboxylate* (**28**). From **38** and **4** as bright yellow crystals in 87% yield. M.p. 153–156° (AcOEt). IR: 1713*s*, 1666*s*, 1628*m*, 1590*m*, 1495*s*, 1245*s*, 1195*s*, 1037*s*, 785*m*, 698*m*. ^{1}H-NMR (80 MHz): 4.00 (*s*, CH_3O); 7.29 (*d*, *J* = 5.5, H–C(3)); 7.44 (*d*, *J* = 7.5, H–C(4)); 7.20–7.57 (*m*, 3 arom. H); 7.80 (*d*, *J* = 5.5, H–C(2)); 7.64–7.93 (*m*, 2 arom. H); 8.36 (*s*, H–C(9)); 9.35 (*d*, *J* = 7.5, H–C(5)). MS: 335 (100, M^+), 307 (52), 276 (48), 247 (26), 145 (37), 123 (34).

4.4. *Methyl 10-Chloro-6,7-dihydro-4-oxo-3-phenyl-4*H*-benzo[*a*]quinolizine-1-carboxylate* (**42**) *and -2-carboxylate*. From **41** and **4**, **42** as yellow crystals in 83% yield. M.p. 134.5–135° (AcOEt). IR: 1710*s*, 1650*s*, 1534*m*, 1252*s*, 1238*s*, 792*m*, 697*m*. ^{1}H-NMR (80 MHz): 2.97 (*t*, *J* = 6.0, 2 H–C(7)); 3.79 (*s*, CH_3O); 4.25 (*t*, *J* = 6.0, 2 H–C(6)); 7.15–7.50 (*m*, 6 arom. H); 7.58–7.80 (*m*, 2 arom. H); 7.87 (*s*, H–C(2)). MS: 365 (100, M^+), 350 (33), 306 (18).

After having isolated **42**, further elution of the column (toluene/AcOEt 9:1) afforded the regioisomer *methyl 10-chloro-6,7-dihydro-4-oxo-3-phenyl-4*H*-benzo[*a*]quinolizine-2-carboxylate* in 2% yield. M.p. 141–141.5°. IR: 1733*s*, 1637*s*, 1580*s*, 1528*m*, 1232*m*, 772*m*, 695*m*. ^{1}H-NMR (80 MHz): 2.99 (*t*, *J* = 6.5, 2 H–C(7)); 3.59 (*s*, CH_3O); 4.31 (*t*, *J* = 6.5, 2 H–C(6)); 6.88 (*s*, H–C(1)); 7.13–7.45 (*m*, 7 arom. H); 7.74 (*d*, *J* = 2.0, H–C(11)). MS: 365 (100, M^+), 350 (35), 306 (21).

4.5. *Methyl 9-Chloro-6,7-dihydro-4-oxo-3-phenyl-4*H*-benzo[*a*]quinolizine-1-carboxylate* (**46**). From 8-chloro-5,6-dihydro-2-phenylthiazolo[2,3-*a*]isoquinolinium 3-oxide and **4** in 90% yield. M.p. 178–179° (AcOEt). IR: 1708*s*, 1640*s*, 1530*s*, 1252*s*, 790*m*, 695*m*. ^{1}H-NMR (90 MHz): 2.95 (*t*, *J* = 6.5, 2 H–C(7)); 3.74 (*s*, CH_3O); 4.24 (*t*, *J* = 6.5, 2 H–C(6)); 7.15–7.57 (*m*, 6 arom. H); 7.62–7.84 (*m*, 2 arom. H); 7.93 (*s*, H–C(2)). MS: 365 (100, M^+), 350 (30), 334 (10), 306 (19).

4.6. *Methyl 10-Chloro-3-(4-chlorophenyl)-6,7-dihydro-4-oxo-4*H*-benzo[*a*]quinolizine-1-carboxylate* (**47**) *and -2-carboxylate*. From 9-chloro-2-(4-chlorophenyl)-5,6-dihydrothiazolo[2,3-*a*]isoquinolin-4-ium 3-oxide [11] and **4**, **47** in 94% yield after separation from the regioisomer by chromatography (silica gel, toluene/AcOEt 9:1). M.p. 206–207.5° (AcOEt/(i-Pr)$_2$O). IR: 1730*s*, 1658*s*, 1530*m*, 832*m*, 815*m*. ^{1}H-NMR (80 MHz): 2.96 (*t*, *J* = 6.0,

2 H–C(7)); 3.78 (*s*, CH_3O); 4.23 (*t*, *J* = 6.0, 2 H–C(6)); 7.15–7.47 (*m*, 5 arom. H); 7.59–7.79 (*m*, 2 arom. H); 7.87 (*s*, H–C(2)). MS: 399 (100, M^+), 384 (22), 364 (9), 340 (11).

The regioisomer 2-carboxylate was obtained in 2% yield. M.p. 206–207.5° (EtOH). IR: 1736*s*, 1642*s*, 1590*s*, 1538*s*, 1250*s*, 848*m*. ^{1}H-NMR (80 MHz): 2.98 (*t*, *J* = 6.5, 2 H–C(7)); 3.76 (*s*, CH_3O); 4.29 (*t*, *J* = 6.5, 2 H–C(6)); 6.88 (*s*, H–C(1)); 7.12–7.45 (*m*, 6 arom. H); 7.72 (*d*, *J* = 2.0, H–C(11)). MS: 399 (100, M^+), 384 (20), 340 (17).

4.7. *Methyl 6,7-Dihydro-4-oxo-3-phenyl-4*H*-benzo[*a*]quinolizine-1-carboxylate* (**48**). From 5,6-dihydro-2-phenylthiazolo[2,3-*a*]isoquinolin-4-ium 3-oxide and **4** in 93% yield. M.p. 196.5–197.5° (EtOH). IR: 1714*s*, 1652*s*, 1530*s*, 1250*s*, 790*m*, 770*m*, 748*m*, 700*m*. ^{1}H-NMR (60 MHz): 3.0 (*t*, *J* = 6.0, 2 H–C(7)); 3.76 (*s*, CH_3O); 4.27 (*t*, *J* = 6.0, 2 H–C(6)); 7.23–7.90 (*m*, 9 arom. H); 7.92 (*s*, H–C(2)). MS: 331 (100, M^+), 316 (17), 272 (8).

4.8. *Methyl 10-Chloro-4-oxo-3-phenyl-4*H*-benzo[*a*]quinolizine-1-carboxylate* (**54**). From 9-chloro-2-phenylthiazolo[2,3-*a*]isoquinolin-4-ium 3-oxide and **4** in 81% yield. Bright yellow crystals. M.p. 169–170° (AcOEt). UV: 422 (4.28), 351 (3.67), 316 (4.23), 290 (3.84), 245 (4.50), 211 (4.36). IR: 1715*s*, 1674*s*, 1637*s*, 1594*m*, 1506*s*, 1246*s*, 838*m*. ^{1}H-NMR (270 MHz): 3.97 (*s*, CH_3O); 7.22 (*dd*, *J* = 7.8, 0.7, H–C(7)); 7.23–7.53 (*m*, 3 arom. H); 7.66 (*m*, H–C(8), H–C(9)); 7.79–7.86 (*m*, 2 arom. H); 7.93 (*dd*, *J* = 1.0, 0.7, H–C(11)); 8.17 (*s*, H–C(2)); 9.03 (*d*, *J* = 7.8, H–C(6)). MS: 363 (100, M^+), 335 (30), 332 (9), 304 (50), 276 (19), 240 (33), 173 (21), 121 (22).

5. *Saponification of Methyl Esters.* 5.1. *4,5-Dihydro-7-oxo-8-phenyl-7*H*-thieno[2,3-*a*]quinolizine-10-carboxylic Acid* (**16**). To a soln. of NaOH (17.7 g, 0.44 mol) in MeOH (900 ml) and H_2O (20 ml), **14** (112.6 g, 0.33 mol) was added and refluxed under Ar for 24 h. While **14** dissolved slowly, the sodium salt of **16** precipitated. After evaporation, the residue was dissolved in H_2O, washed with $CHCl_3$, and treated with charcoal. Acidification with 2N HCl (223.5 ml) gave yellow **16** which was filtered off, washed with H_2O, and dried at 80–90°/12 Torr: 106 g (98.4%) of pure **16**. M.p. 210–210.5° (dec.). IR: 3430*m*, 1710*s*, 1640*s*, 1530*m*, 790*m*, 700*m*. ^{1}H-NMR (80 MHz, DMSO): 3.00 (*t*, *J* = 7.0, 2 H–C(4)); 4.32 (*t*, *J* = 7.0, 2 H–C(5)); 7.12 (*d*, *J* = 5.5, H–C(3)); 7.30–7.62 (*m*, 3 arom. H); 7.62–7.90 (*m*, 2 arom. H); 7.84 (*s*, H–C(9)); 7.86 (*d*, *J* = 5.5, H–C(2)); 13.35 (br., COOH). MS: 323 (19, M^+), 279 (94), 278 (100), 250 (25).

Similarly were prepared:

5.2. *5,6-Dihydro-8-oxo-9-phenyl-8*H*-pyrido[1,2-*d*]thieno[2,3-f][1,4]thiazepine-11-carboxylic Acid.* From **5** in 92% yield as yellow crystals. M.p. 265–266° (dec.; MeOH/DMF). UV: 358 (4.19), 306 (3.78), 287 (3.84), 273 (3.82), 232 (sh, 4.19). IR: 1706*s*, 1649*s*, 1605*s*, 1596*s*, 1541*s*, 1494*m*, 1195*s*, 735*m*, 697*m*. ^{1}H-NMR (60 MHz, DMSO): 3.32–3.60 (*m*, 2 H–C(5), 2 H–C(6)); 7.22 (*d*, *J* = 5.5, H–C(3)); 7.30–7.57 (*m*, 3 arom. H); 7.64–7.87 (*m*, 2 arom. H); 7.95 (*d*, *J* = 5.5, H–C(2)); 7.97 (*s*, H–C(10)); 13.00 (br., COOH). MS: 355 (96, M^+), 322 (72), 311 (100), 271 (98).

5.3. *7-Oxo-8-phenyl-7*H*-thieno[2,3-*a*]quinolizine-10-carboxylic Acid.* From **28** as bright yellow crystals in 94% yield. M.p. 190–192° (dec.). ^{1}H-NMR (60 MHz, $CDCl_3$/DMSO 1:1): 7.46 (*d*, *J* = 5.0, H–C(3)); 7.70 (*d*, *J* = 8.0, H–C(4)); 7.20–7.88 (*m*, 5 arom. H); 8.06 (*d*, *J* = 5.0, H–C(2)); 8.43 (*s*, H–C(9)); 9.30 (*d*, *J* = 8.0, H–C(5)).

5.4. *10-Chloro-6,7-dihydro-4-oxo-3-phenyl-4*H*-benzo[*a*]quinolizine-1-carboxylic Acid.* From **42** in 93% yield. M.p. 280° (dec.). IR: 3430*m*, 1726*m*, 1620*s*, 1595*s*, 1530*m*, 790*m*, 700*m*. ^{1}H-NMR (400 MHz, DMSO): 2.97 (*t*, *J* = 6.0, 2 H–C(7)); 4.11 (*t*, *J* = 6.0, 2 H–C(6)); 7.33–7.38 (*m*, 1 arom. H); 7.40–7.46 (*m*, 3 arom. H); 7.50 (*dd*, *J* = 8.5, 2.0, H–C(9)); 7.67 (*d*, *J* = 2.0, H–C(11)); 7.73–7.76 (*m*, 2 arom. H); 7.82 (*s*, H–C(2)); 13.00 (br., COOH). MS: 351 (75, M^+), 307 (78), 69 (100).

5.5. *10-Chloro-4-oxo-3-phenyl-4*H*-benzo[*a*]quinolizine-1-carboxylic Acid.* From **54** as bright yellow crystals in 96% yield. M.p. 221–222° (dec.; acetone). UV: 421 (4.28), 345 (3.64), 316 (4.22), 290 (3.87), 244 (4.50), 211 (4.37). IR: 1685*s*, 1613*s*, 1584*s*, 1503*s*, 1253*s*. ^{1}H-NMR (270 MHz, DMSO): 7.36–7.52 (*m*, 3 arom. H); 7.54 (*d*, *J* = 8.0, H–C(7)); 7.80–7.91 (*m*, H–C(9), 2 arom. H); 7.97 (*d*, *J* = 8.5, H–C(8)); 8.17 (*s*, H–C(2)); 8.20 (*d*, *J* = 2.5, H–C(11)); 8.93 (*d*, *J* = 8.0, H–C(6)); 13.65 (br., COOH). MS: 349 (100, M^+), 321 (54), 305 (94), 277 (98), 241 (46), 120 (52).

6. *Preparation of Carboxamides.* 6.1. *10-[(*cis*-2,6-Dimethylmorpholin-4-yl)carbonyl]-4,5-dihydro-8-phenyl-7*H*-thieno[2,3-*a*]quinolizin-7-one* (**17**). Acid **16** (2.6 g, 8 mmol) was added to $SOCl_2$ (8 ml) and the mixture stirred for 1 h at r.t. Excess $SOCl_2$ was evaporated. The residue was dried for 1 h and taken up in toluene (130 ml), treated with *cis*-2,6-dimethylmorpholine (0.6 ml, 8 mmol) and with an excess of Et_3N (4.16 ml, 30 mmol). The mixture was kept overnight at r.t., treated with H_2O, and extracted with $CHCl_3$. The org. layer was dried (Na_2SO_4) and evaporated to give a crystalline residue which was chromatographed on silica gel (toluene/AcOEt 4:1) to yield, after recrystallization from AcOEt/hexane, **17** (1.32 g, 39%). M.p. 221–222°. IR: 1650*s*, 1600*m*, 1575*m*, 1524*w*, 1499*m*. ^{1}H-NMR (270 MHz, mixture of rotamers): 1.05, 1.09 (2*d*, *J* = 6.0, CH_3CH); 1.27 (*d*, *J* = 6.0, CH_3CH); 2.50–2.90 (*m*, 2 H); 2.99–3.05 (*m*, 2 H); 3.36–3.76 (*m*, 3 H); 4.21–4.36 (*m*, 1 H); 4.56–4.73 (*m*, 2 H); 6.98 (*d*, *J* = 5.0, H–C(3)); 7.38–7.56 (*m*, 5 arom. H); 7.69–7.73 (*m*, 2 arom. H). MS: 420 (64, M^+), 306 (100).

Similarly was prepared:

6.2. *4,5-Dihydro-10-[(morpholin-4-yl)carbonyl]-8-phenyl-7*H-*thieno[2,3-a]quinolizin-7-one* (**18**). From **16** and morpholine in 88% yield. M.p. 214–215° (dioxane/Et_2O). IR: 1649*s*, 1625*m*, 1539*m*. ^{1}H-NMR (250 MHz): 2.97–3.05 (*m*, 2 H); 3.25–3.35 (*m*, 1 H); 3.40–3.50 (*m*, 1 H); 3.54–3.58 (*m*, 2 H); 3.69–3.79 (*m*, 2 H); 3.83–3.98 (*m*, 2 H); 4.15–4.26 (*m*, 1 H); 4.64–4.74 (*m*, 1 H); 6.98 (*d*, *J* = 4.0, H–C(3)); 7.26–7.47 (*m*, 5 arom. H); 7.66–7.72 (*m*, 2 arom. H). MS: 392 (50, M^+), 307 (20), 306 (100).

6.3. N,N-*Diethyl-4,5-dihydro-7-oxo-8-phenyl-7*H-*thieno[2,3-a]quinolizine-10-carboxamide* (**19**). To a soln. of **16** (2.0 g, 6.2 mmol) and 2-chloro-1-methylpyridinium iodide [14] (1.9 g, 7.4 mmol) in CH_2Cl_2 (60 ml), Bu_3N (3.6 ml, 15 mmol) and Et_2NH (0.65 ml, 6.25 mmol) were added. The mixture was refluxed for 1.5 h under Ar (→ clear soln.). After diluting with Et_2O (140 ml), washing with 2N HCl, H_2O, and brine, drying ($MgSO_4$), and evaporation, the residue (3,7 g) was chromatographed (silica gel (180 g), toluene/dioxane 9:1) to give, after crystallization from i-PrOH, pure **19** (1.8 g, 76.7%). M.p. 177–177.5°. IR: 1640*s*, 1596*s*, 1540*s*, 1520*s*, 792*m*, 700*m*. ^{1}H-NMR (60 MHz): 1.02 (*t*, *J* = 7.0, CH_3CH_2); 1.32 (*t*, *J* = 7.0, CH_3CH_2); 3.00 (*t*, *J* = 7.0, 2 H–C(4)); 3.30 (*q*, *J* = 7.0, CH_3CH_2); 3.61 (*q*, *J* = 7.0, CH_3CH_2); 3.85–5.0 (*m*, 2 H–C(5)); 6.95 (*d*, *J* = 5.0, H–C(3)); 7.23–7.53 (*m*, 3 arom. H); 7.35 (*s*, H–C(9)); 7.43 (*d*, *J* = 5.0, H–C(2)); 7.55–7.85 (*m*, 2 arom. H). MS: 378 (60, M^+), 306 (100), 278 (32).

6.4. *4,5-Dihydro-7-oxo-8-phenyl-7*H-*thieno[2,3-a]quinolizine-10-carboxamide* (**20**) was prepared as described in *6.1* in 95.5% yield. M.p. 281–282° (EtOH). IR: 3370*s*, 3180*m*, 1650*s*, 1608*s*, 1530*m*, 1510*m*, 695*m*. ^{1}H-NMR (60 MHz, DMSO): 2.95 (*t*, *J* = 6.5, 2 H–C(4)); 4.30 (*t*, *J* = 6.5, 2 H–C(5)); 7.10 (*d*, *J* = 5.0, H–C(3)); 7.29–7.50 (*m*, 3 arom. H); 7.56 (*s*, H–C(9)); 7.65 (br., 1 H, NH_2); 7.70–7.88 (*m*, 2 arom. H); 7.79 (*d*, *J* = 5.0, H–C(2)); 8.34 (br., 1 H, NH_2). MS: 322 (100, M^+), 304 (22), 278 (18).

Similarly were prepared:

6.5. N-*[2-(Dimethylamino)ethyl]-4,5-dihydro-7-oxo-8-phenyl-7*H-*thieno[2,3-a]quinolizine-10-carboxamide Hydrochloride* (**21**·HCl). From **16** and 2-(dimethylamino)ethylamine followed by formation of the hydrochloride salt with HCl/MeOH in 33% yield. M.p. 257–259° (MeOH/Et_2O). IR: 3269*m*, 2426*w*, 1634*s*, 1599*m*, 1536*m*. ^{1}H-NMR (90 MHz, CD_3OD): 2.94 (*s*, $(CH_3)_2N$); 2.97 (*t*, *J* = 7.0, CH_2NHCO); 3.36 (*t*, *J* = 5.0, 2 H–C(4)); 3.68 (*t*, *J* = 5.0, 2 H–C(5)); 4.30 (*t*, *J* = 7.0, CH_2NH^+); 7.03 (*d*, *J* = 5.0, H–C(3)); 7.30–7.43 (*m*, 3 arom. H); 7.58–7.68 (*m*, 2 arom. H); 7.61 (*d*, *J* = 5.0, H–C(2)); 7.66 (*s*, H–C(9)). MS: 393 (2, M^+), 322 (12), 58 (100).

6.6. *10-[(*cis-*2,6-Dimethylmorpholin-4-yl)carbonyl]-8-phenyl-7*H-*thieno[2,3-a]quinolizin-7-one* (**29**) in 76% yield as bright yellow crystals. M.p. > 280° (toluene). UV: 420 (4.37), 324 (3.27), 305 (4.32), 283 (4.01), 264 (4.14), 256 (4.12), 230 (4.34), 220 (4.33). IR: 1649*s*, 1616*s*, 1500*s*, 1446*s*, 1262*m*, 1083*m*, 790*w*, 645*w*. ^{1}H-NMR (80 MHz; *ca.* 1:1 mixture of rotamers): 1.02 (*d*, *J* = 6.0, CH_3CH); 1.31 (*d*, *J* = 6.8, CH_3CH); 2.52–3.05 (*m*, 2 H); 3.20–4.11 (br. *m*, 3 H); 4.55–4.96 (br. *m*, 1 H); 7.33–7.56 (*m*, 5 arom. H); 7.54, 7.58 (2*s*, H–C(9)); 7.59–7.72 (*m*, 3 arom. H); 9.20, 9.23 (2*d*, *J* = 7.5, H–C(5)). MS: 418 (84, M^+), 304 (100), 277 (18), 276 (16), 248 (25).

6.7. *10-[(Morpholin-4-yl)carbonyl]-8-phenyl-7*H-*thieno[2,3-a]quinolizin-7-one* (**30**) in 77% yield as bright yellow crystals. M.p. 271–272° (dec.; EtOH/DMF). UV: 419 (4.18), 324 (3.09), 306 (4.13), 283 (3.83), 265 (3.97), 256 (3.95), 232 (4.17), 221 (4.14). IR: 1656*s*, 1618*s*, 1486*s*, 1445*s*, 1285*m*, 1271*m*, 1247*m*, 1115*s*. ^{1}H-NMR (90 MHz, DMSO): 3.21–3.56 (*m*, 4 H); 3.75–3.92 (*m*, 4 H); 7.30–7.55 (*m*, 3 arom. H); 7.62 (*d*, *J* = 5.0, H–C(3)); 7.69 (*d*, *J* = 7.5, H–C(4)); 7.81–7.97 (*m*, 2 arom. H); 7.95 (*s*, H–C(9)); 8.21 (*d*, *J* = 5.0, H–C(2)); 9.15 (*d*, *J* = 7.5, H–C(5)). MS: 390 (72, M^+), 304 (100), 276 (15), 248 (45).

6.8. N-*(2-Methoxyethyl)-7-oxo-8-phenyl-7*H-*thieno[2,3-a]quinolizine-10-carboxamide* (**31**) in 79% yield as bright yellow crystals. M.p. 201–203° (AcOEt). UV: 418 (4.37), 325 (3.30), 306 (4.30), 284 (3.98), 266 (4.15), 255 (4.11), 235 (4.32), 220 (4.27). IR: 3266*m*, 1632*s*, 1596*m*, 1546*s*, 1488*s*, 1290*s*, 783*m*, 693*m*. ^{1}H-NMR (80 MHz): 3.40 (*s*, CH_3O), 3.61–3.80 (*m*, 4 H); 7.16 (*d*, *J* = 7.0, H–C(4)); 7.26 (*d*, *J* = 5.5, H–C(3)); 7.02–7.52 (*m*, 3 arom. H); 7.68 (*d*, *J* = 5.5, H–C(2)); 7.51–7.79 (*m*, 2 arom. H); 7.80 (*s*, H–C(9)); 9.07 (*d*, *J* = 7.0, H–C(5)). MS: 378 (100, M^+), 320 (22), 304 (39), 277 (21), 276 (20), 248 (26), 145 (17).

6.9. N-*(3-Methoxypropyl)-7-oxo-8-phenyl-7*H-*thieno[2,3-a]quinolizine-10-carboxamide* (**32**) in 87% yield as bright yellow crystals. M.p. 188–189° (AcOEt). UV: 418 (4.37), 325 (3.29), 306 (4.30), 283 (3.97), 265 (4.14), 255 (4.10), 235 (4.32), 220 (4.27). IR: 3285*m*, 1659*s*, 1631*s*, 1598*m*, 1544*s*, 1488*s*, 1115*m*, 1078*m*, 783*m*, 696*m*. ^{1}H-NMR (80 MHz): 2.00 (*quint.*, *J* = 6.0, $CH_2CH_2CH_2$); 3.34 (*s*, CH_3O); 3.40–3.81 (*m*, $CH_2CH_2CH_2$); 7.17 (*d*, *J* = 7.5, H–C(4)); 7.30 (*d*, *J* = 5.0, H–C(3)); 7.15–7.52 (*m*, 3 arom. H); 7.75 (*d*, *J* = 5.0, H–C(2)); 7.59–7.89 (*m*, 2 arom. H); 7.81 (*s*, H–C(9)); 9.02 (*d*, *J* = 7.5, H–C(5)). MS: 392 (100, M^+), 303 (26), 276 (20), 248 (22), 145 (16).

6.10. *10-Chloro-6,7-dihydro-1-[(morpholin-4-yl)carbonyl]-3-phenyl-4*H-*benzo[a]quinolizin-4-one* (**43**). From 10-chloro-6,7-dihydro-4-oxo-3-phenyl-4*H*-benzo[*a*]quinolizine-1-carboxylic acid and morpholine in 55% yield. M.p. 244–247°. IR: 1650*s*, 1631*m*. ^{1}H-NMR (250 MHz): 2.63–3.08 (*m*, 4 H); 3.17–3.26 (*m*, 1 H); 3.37–3.46 (*m*, 1 H); 3.56–3.79 (*m*, 5 H); 5.03 (*ddd*, *J* = 14.0, 4.8, 4.8, 1H, CH_2O); 7.26–7.42 (5 arom. H); 7.55 (*s*, H–C(2)); 7.69–7.76 (*m*, 3 arom. H). MS: 420 (40, M^+), 334 (100).

6.11. *10-Chloro-1-[(*cis*-2,6-dimethylmorpholin-4-yl)carbonyl]-6,7-dihydro-3-phenyl-4*H*-benzo[a]quinolizin-4-one* (**44**) from 10-chloro-6,7-dihydro-4-oxo-3-phenyl-4*H*-benzo[*a*]quinolizine-1-carboxylic acid and *cis*-2,6-dimethylmorpholine in 25% yield. M.p. 163–165°. IR: 1635*s*, 1610*m*, 1600*m*, 1566*m*. ^{1}H-NMR (400 MHz, mixture of rotamers): 0.90, 0.98 (2*d*, J = 6.0, CH_3CH); 1.22 (*d*, J = 6.0, CH_3CH); 1.92–2.50 (*m*, 2 H); 2.67–3.77 (*m*, 6 H); 4.60 (*m*, 1 H); 4.87, 5.09 (2*m*, 1 H); 7.26–7.59 (*m*, 7 arom. H); 7.73–7.80 (*m*, 2 arom. H). MS: 448 (40, M^+), 334 (100).

6.12. *10-Chloro-*N*-[2-(dimethylamino)ethyl]-6,7-dihydro-4-oxo-3-phenyl-4*H*-benzo[a]quinolizine-1-carboxamide Hydrochloride* (**45**·HCl) from 10-chloro-6,7-dihydro-4-oxo-3-phenyl-4*H*-benzo[*a*]quinolizine-1-carboxylic acid and 2-(dimethylamino)ethylamine, followed by formation of the hydrochloride salt with methanolic HCl in 67% yield. M.p. 158–161° (MeOH/Et_2O). IR: 1636*s*, 1530*m*. ^{1}H-NMR (250 MHz): 2.69 (*s*, $(CH_3)_2N$); 3.09 (br., 4 H); 3.71 (br., 2 H); 4.21 (br., 2 H); 7.26–7.40 (*m*, 5 arom. H); 7.56 (*s*, 1 H); 7.73 (*m*, 3 H); 8.50 (br., 1 H); 11.59 (br., 1 H). MS: 421 (1, M^+), 350 (4), 334 (60), 58 (100).

6.13. *10-Chloro-1-{[(*S*)-2-(methoxymethyl)pyrrolidin-1-yl]carbonyl}-3-phenyl-4*H*-benzo[a]quinolizin-4-one* (**55**) in 82% yield as bright yellow crystals. M.p. 137–139° (cyclohexane/EtOH). $[\alpha]_D^{20} = -148.6$ (c = 0.5, $CHCl_3$). UV: 418 (4.28), 341 (3.58), 314 (4.22), 288 (3.86), 275 (4.16), 271 (4.15), 243 (4.50), 220 (4.39). IR: 1660*s*, 1626*s*, 1601*m*, 1504*s*, 1421*s*, 1298*m*, 1107*m*, 838*m*, 763*m*, 700*m*. ^{1}H-NMR (270 MHz, mixture of rotamers): 1.51–2.21 (*m*, CH_2CH_2); 3.05, 3.38, 3.44 (3*s*, CH_3O); 2.85–4.15, 4.49–4.67 (*m*, CH_2O, CHN, CH_2N); 7.09, 7.12 (2*d*, J = 8.0, H–C(7)); 7.30–7.55 (*m*, 3 arom. H); 7.64 (*s*, H–C(8), H–C(9)); 7.75–7.92 (*m*, 3 arom. H); 8.08, 8.21 8.42 (3*s*, H–C(2)); 9.03 (*d*, J = 8.0, H–C(6)). MS: 466 (29, M^+), 332 (100), 276 (22), 240 (12).

6.14. *10-Chloro-1-{[(*R*)-2-(methoxymethyl)pyrrolidin-1-yl]carbonyl}-3-phenyl-4*H*-benzo[a]quinolizin-4-one* (**56**) in 75% yield as bright yellows crystals. M.p. 137–140° (cyclohexane/EtOH). $[\alpha]_D^{20} = +152.2$ (c = 0.5, $CHCl_3$). UV, IR, ^{1}H-NMR, MS: see *6.13*.

6.15. *10-Chloro-1-[(3-methoxyazetidin-1-yl)carbonyl]-3-phenyl-4*H*-benzo[a]quinolizin-4-one* (**57**) in 67% yield as bright yellow crystals. M.p. 175–177° (AcOEt). UV: 418 (4.29), 343 (3.62), 315 (4.23), 289 (3.88), 244 (4.52), 219 (4.40). IR: 1658*s*, 1636*s*, 1601*m*, 1505*s*, 1452*s*, 1127*m*, 1102*m*, 839*w*, 718*w*. ^{1}H-NMR (270 MHz, DMSO): 3.15 (*s*, CH_3O); 3.50–3.66, 3.80–4.11, 4.31–4.43 (3*m*, CH_2NCH_2); 4.15–4.31 (*m*, CHO); 7.33–7.53 (*m*, 4 arom. H); 7.84–8.00 (*m*, 4 arom. H); 8.26 (*s*, H–C(2)); 8.96 (*d*, J = 8.1, H–C(6)). MS: 418 (53, M^+), 332 (100), 276 (22), 241 (9), 240 (9).

7. *Preparation of Sulfoxides.* 7.1. *Methyl 5,6-Dihydro-4,8-dioxo-9-phenyl-8*H*-pyrido[1,2-d]thieno[2,3-f][1,4]thiazepine-11-carboxylate* (**7**). A soln. of 3-$ClC_6H_4CO_3H$ (22.0 g, 0.1 mol; purity *ca.* 80%) in CH_2Cl_2 (450 ml) was added dropwise within 25 min to a cooled soln. (0–2°) of **5** (37.6 g, 0.1 mol) in CH_2Cl_2 (750 ml). The mixture was warmed up to r.t., washed twice with sat. $NaHCO_3$ soln. (800 ml), H_2O (800 ml), and dried (Na_2SO_4). The solvent was evaporated and the residue chromatographed on silica gel. Elution with CH_2Cl_2/Et_2O 9:1 furnished pure **7** which was recrystallized from hexane/AcOEt/Et_2O 2:1:1 to give pale yellow **7** (25.8 g, 67%)[6]. M.p. 135–137°. UV: 358 (4.22), 310 (4.05), 257 (4.15), 249 (4.13), 242 (4.15), 237 (4.14). IR: 1713*s*, 1655*s*, 1601*m*, 1550*m*, 1496*w*, 1289*m*, 1275*w*, 1256*m*, 1055*m*, 743*w*, 700*w*. ^{1}H-NMR (80 MHz): 3.72 (*s*, CH_3O); 2.81–5.50 (br., NCH_2CH_2SO); 7.42 (*d*, J = 5.0, H–C(3)); 7.25–7.51 (*m*, 3 arom. H); 7.70 (*d*, J = 5.0, H–C(2)); 7.54–7.82 (*m*, 2 arom. H); 7.98 (*s*, H–C(10)). MS: 385 (100, M^+), 368 (65), 336 (15), 305 (34).

Similarly were prepared:

7.2. *Methyl 5,6-Dihydro-4,8-dioxo-9-phenyl-8*H*-pyrido[1,2-d]thieno[2,3-f][1,4]thiazepine-10-carboxylate* (**10**) in 68% yield as pale yellow crystals. M.p. 194–195°. UV: 370 (4.23), 309 (3.52), 278 (3.82), 260 (3.78). IR: 1741*s*, 1646*s*, 1595*s*, 1545*m*, 1493*w*, 1229*s*, 1024*m*, 772*m*. ^{1}H-NMR (80 MHz): 3.59 (*s*, CH_3O); 3.24–3.56, 3.91–4.27 (2*m*, CH_2SO); 4.26–4.95 (*m*, CH_2N); 6.87 (*s*, H–C(11)); 7.35–7.45 (*m*, 5 arom. H); 7.52, 7.62 (*AB*, J = 5.0, H–C(2), H–C(3)). MS: 385 (100, M^+), 368 (63), 336 (28).

7.3. *11-Chloro-5,6-dihydro-9-phenyl-8*H*-pyrido[1,2-d]thieno[2,3-f][1,4]thiazepine-4,8-dione* (**9**) in 69% yield as yellow crystals. M.p. 209–211° (MeCN). UV: 374 (4.24), 362 (3.46), 273 (3.92), 250 (3.91). IR: 1644*s*, 1585*m*, 1572*m*, 1537*m*, 1478*w*, 1060*s*, 753*w*, 697*m*. ^{1}H-NMR (60 MHz): 3.02–5.53 (br., NCH_2CH_2SO); 7.31 (*d*, J = 5.0, H–C(3)); 7.32–7.94 (*m*, 5 arom. H); 7.61 (*s*, H–C(10)); 7.78 (*d*, J = 5.0, H–C(2)). MS: 361 (65, M^+), 345 (65), 310 (100), 283 (60).

8. *5,6-Dihydro-9-phenyl-8*H*-pyrido[1,2-d]thieno[2,3-f][1,4]thiazepin-8-one* (**8**). For 40 min, 5,6-dihydro-8-oxo-9-phenyl-8*H*-pyrido[1,2-*d*]thieno[2,3-*f*][1,4]thiazepine-11-carboxylic acid (*cf. 5.2;* 3.43 g, 9.6 mmol) was subjected to thermolysis at 285°/0.5 Torr. Crude **8** was purified by chromatography (CH_2Cl_2/Et_2O 2:1) to give, after recrystallization from MeCN, pure **8** (2.56 g, 85%). Yellow crystals. M.p. 139–141°. UV: 369 (4.28), 289

[6]) Traces of less polar sulfone were also isolated.

(3.66), 274 (3.73); 236 (4.03), 228 (4.02). IR: 1641*s*, 1586*m*, 1569*m*, 1550*s*, 1490*m*, 759*m*, 722*m*, 704*m*. ^{1}H-NMR (80 MHz): 3.34–3.60 (*m*, CH_2S); 4.41–4.62 (*m*, CH_2N); 6.41 (*d*, J = 7.5, H–C(11)); 7.03 (*d*, J = 5.5, H–C(3)); 7.43 (*d*, J = 5.5, H–C(2)); 7.15–7.46 (*m*, 3 arom. H); 7.51 (*d*, J = 7.5, H–C(10)); 7.65–7.72 (*m*, 2 arom. H). MS: 311 (85, M^+), 278 (100), 250 (13).

9. *11-Chloro-5,6-dihydro-9-phenyl-8*H-*pyrido[1,2-*d*]thieno[2,3-*f*][1,4]thiazepin-8-one*. To a suspension of *N*-chlorosuccinimide (2.34 g, 17.5 mmol) in CCl_4 (48 ml), **8** (4.95 g, 15.9 mmol) was added and stirred for 2.5 h at r.t. Then, more *N*-chlorosuccinimide (0.21 g, 1.6 mmol) was added. The solvent was evaporated and the residue chromatographed (silica gel (500 g), CH_2Cl_2/Et_2O 19:1). Recrystallization from MeCN furnished the title compound as yellow crystals (2.8 g, 51%). M.p. 179°. UV: 372 (4.23), 304 (3.58), 272 (sh, 3.85), 249 (sh, 3.95). IR: 1640*s*, 1582*m*, 1571*m*, 1534*s*, 1475*w*, 1436*m*, 753*m*, 732*w*, 692*m*. ^{1}H-NMR (270 MHz): 3.04–3.57 (*m*, 3 H, SCH_2CH_2N); 5.10–5.30 (*m*, 1 H, CH_2N); 7.14 (*d*, J = 5.0, H–C(3)); 7.30–7.46 (*m*, 3 arom. H); 7.58 (*d*, J = 5.0, H–C(2)); 7.60 (*s*, H–C(10)); 7.60–7.81 (*m*, 2 arom. H). MS: 345 (80, M^+), 312 (92), 310 (100), 277 (26), 266 (25), 249 (23).

10. *4,5-Dihydro-10-methyl-8-phenyl-7*H-*thieno[2,3-*a*]quinolizin-7-one* (**24**). To **16** (1.29 g, 4 mmol) in dry THF (40 ml) at −15°, 10M $BH_3 \cdot Me_2S$ (0.8 ml, 8 mmol) was added slowly. After having come to r.t. the mixture was refluxed for 2 h. Excess BH_3 was decomposed by cautiously adding MeOH and 2N HCl. Extraction with $CHCl_3$, washing of the org. layer with Na_2CO_3 soln. and brine, drying ($MgSO_4$), and evaporation gave, after chromatography (silica gel (150 g), toluene/dioxane 9:1) and crystallization from AcOEt/$(i\text{-}Pr)_2O$, pure **24** (0.66 g, 56.5%). M.p. 80.5–81°. IR: 1630*s*, 1585*m*, 780*m*, 690*m*. ^{1}H-NMR (80 MHz): 2.50 (*s*, CH_3); 3.00 (*t*, J = 6.8, 2 H–C(4)); 4.50 (*t*, J = 6.8, 2 H–C(5)); 7.03 (*d*, J = 5.0, H–C(3)); 7.27–7.60 (*m*, 3 arom. H); 7.52 (*d*, J = 5.0, H–C(2)); 7.70–7.90 (*m*, 2 H). MS: 293 (100, M^+), 278 (19).

11. *4,5-Dihydro-10-(hydroxymethyl)-8-phenyl-7*H-*thieno[2,3-*a*]quinolizin-7-one* (**23**). The acylchloride **25** prepared as described in *6.1* from **16** (14.2 g, 44 mmol) and $SOCl_2$ (88 ml) was dried at r.t./0.1 Torr, dissolved in dry THF (135 ml), and slowly added at 20° to a soln. of $NaBH_4$ (3.34 g, 88 mmol) in dry DMF (88 ml). After stirring for 3 h, excess reagent was decomposed by slowly adding 2N HCl (50 ml), while cooling with ice, shortly heated up to *ca.* 80°, and finally neutralized by adding *ca.* 50 ml of 2N NaOH. This soln., after being diluted with H_2O, was extracted with $CHCl_3$/MeOH 9:1. The combined org. layers were washed with brine, dried ($MgSO_4$), and evaporated. From the residue **23** (12.13 g, 89%) was obtained by adding Et_2O/MeOH. M.p. 199–200.5° (MeOH). IR: 3400*m*, 3300*m*, 1623*s*, 1580*s*, 1530*s*, 1510*s*, 1075*s*, 782*m*, 750*m*, 690*m*. ^{1}H-NMR (60 MHz, $CDCl_3$/DMSO): 3.00 (*t*, J = 7.0, 2 H–C(4)); 4.42 (*t*, J = 7.0, 2 H–C(5)); 4.80 (*s*, CH_2O); 7.05 (*d*, J = 5.0, H–C(3)); 7.20–7.90 (*m*, 6 arom. H); 7.57 (*d*, J = 5.0, H–C(2)). MS: 309 (100, M^+), 292 (60), 278 (28).

12. *(4,5-Dihydro-7-oxo-8-phenyl-7*H-*thieno[2,3-*a*]quinolizin-10-yl)methyl Morpholine-4-carboxylate* (**22**). A suspension of **23** (0.59 g, 1.9 mmol) in dioxane (15 ml) was treated under stirring with phenyl chloroformate (0.38 ml, 3 mmol) and pyridine (0.27 ml, 0.335 mmol). After 2.5 h, morpholine (3.04 ml, 35 mmol) was added to the suspension and stirring continued for *ca.* 24 h. The resulting soln. was diluted with $CHCl_3$, washed with 1N HCl, 10% aq. $KHCO_3$ soln., and brine, dried ($MgSO_4$), evaporated, and crystallized from EtOH: pure **22** (0.64 g, 80%). IR: 1702*s*, 1640*s*, 1535*s*, 1083*m*, 788*m*, 698*m*. ^{1}H-NMR (80 MHz): 2.95 (*t*, J = 6.5, 2 H–C(4)); 3.38–3.73 (*m*, 8 H, morpholine); 4.42 (*t*, J = 6.5, 2 H–C(5)); 5.25 (*s*, CH_2O); 7.00 (*d*, J = 5.0, H–C(3)); 7.20–7.80 (*m*, 5 arom. H); 7.47 (*d*, J = 5.0, H–C(2)); 7.61 (*s*, H–C(9)). MS: 422 (22, M^+), 378 (4), 292 (100).

13. *Ring Contractions of Unsaturated Thiazepine Derivatives.* 13.1. *Methyl 5-Chloro-5,6-dihydro-8-oxo-9-phenyl-8*H-*pyrido[1,2-*d*]thieno[2,3-*f*][1,4]thiazepine-11-carboxylate* (**26**). Sulfoxide **7** (13.8 g, 36 mmol) was added within 10 min to $SOCl_2$ (60 ml) at r.t. The soln. initially orange turned yellow and the temp. rose from 22 to 35°. After completion of the reaction (TLC), the solvent was evaporated and the yellow crystals suspended in H_2O (100 ml). After filtration, the residue was purified by chromatography (silica gel, CH_2Cl_2/Et_2O 9:1) to give, after recrystallization from toluene, pure **26** (9.85 g, 68%). M.p. 192–196°. UV: 358 (4.23), 312 (3.75), 284 (3.89), 254 (sh, 4.08), 239 (sh, 4.17). IR: 1717*s*, 1640*s*, 1601*w*, 1576*w*, 1495*m*, 1241*s*, 747*m*, 720*m*. ^{1}H-NMR (60 MHz): 3.26 (*dd*, J = 13.5, 10.5, H–C(6)); 3.73 (*s*, CH_3O); 5.33 (*dd*, J = 13.5, 5.0, H–C(6)); 5.80 (*dd*, J = 10.5, 5.0, H–C(5)); 7.27 (*d*, J = 5.0, H–C(3)); 7.21–7.53 (*m*, 3 arom. H); 7.54–7.90 (*m*, 2 arom. H); 7.66 (*d*, J = 5.0, H–C(2)); 8.02 (*s*, H–C(10)). MS: 403 (100, M^+), 368 (79), 336 (61), 310 (71).

Similarly was prepared:

13.2. *5,11-Dichloro-5,6-dihydro-9-phenyl-8*H-*pyrido[1,2-*d*]thieno[2,3-*f*][1,4]thiazepin-8-one* from **9** in 86% yield as yellow crystals. M.p. 162–164° (AcOEt). UV: 373 (4.25), 314 (3.52), 278 (sh, 3.86), 240 (sh, 3.97). IR: 1645*s*, 1585*m*, 1573*m*, 1476*m*, 731*w*, 694*w*. ^{1}H-NMR (80 MHz): 3.28 (*dd*, J = 13.5, 10.5, H–C(6)); 5.27 (*dd*, J = 13.5, 5.0, H–C(6)); 5.80 (*dd*, J = 10.5, 5.0, H–C(5)); 7.24 (*d*, J = 5.0, H–C(3)); 7.24–7.55 (*m*, 3 arom. H); 7.60 (*s*, H–C(10)); 7.68 (*d*, J = 5.0, H–C(2)); 7.55–7.85 (*m*, 2 arom. H). MS: 379 (80, M^+), 344 (100), 311 (76), 283 (78).

13.3. *Methyl 8-Oxo-9-phenyl-8*H-*pyrido[1,2-*d*]thieno[2,3-*f*][1,4]thiazepine-11-carboxylate* (**27**). To **26** (6.5 g, 16 mmol) in DMSO (60 ml), DBN (3.6 ml, 30 mmol) was added. The mixture was heated to 70–75° for 4 h, cooled to r.t., and poured into H_2O (300 ml). The crude product was filtered off and purified by chromatography on silica gel ($CHCl_3$) to yield, after recrystallization from toluene, pure **27** (3.8 g, 64%). M.p. 207–210°. UV: 370 (4.24), 314 (3.63), 265 (4.21), 247 (4.12), 228 (4.23), 219 (4.22). IR: 1712*s*, 1650*s*, 1623*w*, 1597*w*, 1532*m*, 1247*s*, 751*m*, 702*m*. ^{1}H-NMR (90 MHz): 3.66 (*s*, CH_3O); 6.59 (*d*, J = 7.9, H–C(5)); 6.90 (*d*, J = 5.0, H–C(3)); 7.25 (*d*, J = 7.9, H–C(6)); 7.47 (*d*, J = 5.0, H–C(2)); 7.35–7.54 (*m*, 3 arom. H); 7.65–7.85 (*m*, 2 arom. H); 7.96 (*s*, H–C(10)). MS: 367 (22, M^+), 335 (100), 307 (34), 276 (32).

Similarly was prepared:

13.4. *11-Chloro-9-phenyl-8*H-*pyrido[1,2-*d*]thieno[2,3-*f*][1,4]thiazepin-8-one* in 54% yield as yellow crystals, from 5,11-dichloro-5,6-dihydro-9-phenyl-8*H*-pyrido[1,2-*d*]thieno[2,3-*f*][1,4]thiazepin-8-one (*cf. 13.2*). M.p. 149–151° (AcOEt). UV: 379 (4.25), 314 (3.46), 261 (4.03), 248 (4.01), 214 (sh, 4.30). IR: 1650*s*, 1621*m*, 1586*m*, 1573*w*, 1525*m*, 1482*m*, 723*w*, 699*w*. ^{1}H-NMR (60 MHz): 6.73 (*d*, J = 7.5, H–C(5)); 7.05 (*d*, J = 5.0, H–C(3)); 7.27 (*d*, J = 7.5, H–C(6)); 7.52 (*d*, J = 5.0, H–C(2)); 7.21–7.62 (*m*, 3 arom. H); 7.60–7.91 (*m*, 2 arom. H); 7.69 (*s*, H–C(10)). MS: 343 (48, M^+), 315 (32), 311 (75), 283 (100), 247 (36), 124 (57).

13.5. *Methyl 7-Oxo-8-phenyl-7*H-*thieno[2,3-*a*]quinolizine-10-carboxylate* (**28**, *cf. 4.3*). A suspension of **27** (4.4 g, 12 mmol) in xylene (90 ml) was refluxed for 24 h. The solvent was evaporated and the residue recrystallized from AcOEt: pure **28** (3.0 g, 75%). M.p. 153–156°. UV, IR, ^{1}H-NMR, and MS: identical to those of the product obtained in *4.3*.

Similarly was prepared:

13.6. *10-Chloro-8-phenyl-7*H-*thieno[2,3-*a*]quinolizin-7-one* (**33**) in 52% yield as bright yellow crystals, from 11-chloro-9-phenyl-8*H*-pyrido[1,2-*d*]thieno[2,3-*f*][1,4]thiazepin-8-one (*cf. 13.4*). M.p. 178–180° (AcOEt). UV: 433 (4.39), 424 (sh, 4.37), 323 (3.13), 306 (4.29), 298 (4.16), 295 (4.17), 282 (3.98), 267 (4.11), 257 (4.08), 241 (4.33), 220 (4.13). IR: 1655*s*, 1630*m*, 1596*w*, 1567*w*, 1495*s*, 1275*m*, 780*m*, 698*m*. ^{1}H-NMR (60 MHz): 7.32 (*d*, J = 8.0, H–C(4)); 7.42 (*d*, J = 5.0, H–C(3)); 7.25–7.59 (*m*, 3 arom. H); 7.70–7.88 (*m*, 2 arom. H); 7.82 (*d*, J = 5.0, H–C(2)); 7.95 (*s*, H–C(9)); 9.12 (*d*, J = 8.0, H–C(5)). MS: 311 (85, M^+), 283 (100), 247 (26), 123 (25).

REFERENCES

[1] W. E. Haefely, in 'Allosteric Modulation of Amino Acid Receptors', 'Therapeutic Implications', Eds. E. A. Barnard and E. Costa, Raven Press, Ltd., New York, 1989, pp. 47–69.

[2] H. Möhler, T. Okada, *Science* **1977,** *198,* 849.

[3] C. Braestrup, R. F. Squires, *Proc. Natl. Acad. Sci. U.S.A.* **1977,** *74,* 3805.

[4] K. T. Potts, E. Houghton, U. P. Singh, *J. Org. Chem.* **1974,** *39,* 3627; K. T. Potts, S. Kanemasa, *ibid.* **1979,** *44,* 3803, 3808; K. T. Potts, K. G. Bordeaux, W. R. Kuehnling, R. L. Salsbury, *ibid.* **1985,** *50,* 1666, 1677; K. T. Potts, M. O. Dery, W. A. Juzukonis, *ibid.* **1989,** *54,* 1077.

[5] R. V. Davies, B. Iddon, T. McC. Paterson, M. W. Pickering, H. Suschitzky, M. W. Gittos, *J. Chem. Soc., Perkin Trans. 1* **1976,** 138.

[6] M. Baudy, A. Robert , A. Foucaud, *J. Org. Chem.* **1978,** *43,* 3732.

[7] M. Wilhelm, P. Schmidt, *Helv. Chim. Acta* **1970,** *53,* 1697; W. Ried, E. König, *Liebigs Ann. Chem.* **1972,** *755,* 24; A. H. Jackson, D. N. Johnston, P. V. R. Shannon, *J. Chem. Soc., Chem. Commun.* **1975,** 911; A. Ricci, D. Balucani, A. Fravolini, F. Schiaffella, G. Grandolini, *Gazz. Chim. Ital.* **1977,** *107,* 19; L. Fodor, D. B. MacLean, *Can. J. Chem.* **1987,** *65,* 18; H. Hofmann, H. Fischer, M. Bremer, *Chem. Ber.* **1987,** *120,* 2087; H. Hofmann, H. Fischer, *ibid.* **1988,** *121,* 2147.

[8] W. Herz, L. Tsai, *J. Am. Chem. Soc.* **1953,** *75,* 5122.

[9] M. W. Gittos, M. R. Robinson, J. P. Verge, R. V. Davies, B. Iddon, H. Suschitzky, *J. Chem. Soc., Perkin Trans. 1* **1976,** 33.

[10] F. Eloy, A. Deryckere, *Helv. Chim. Acta* **1969,** *52,* 1755.

[11] U. Fischer, F. Schneider, U. Widmer, Eur. Pat. 183994, June 11, 1986 (*CA:* **1987,** *15,* 134200b).

[12] Y. Girard, J. G. Atkinson, P. C. Bélanger, J. J. Fuentes, J. Rokach, C. Stanley Rooney, D. C. Remy, C. A. Hunt, *J. Org. Chem.* **1983,** *48,* 3220.

[13] J. J. Pommeret, A. Robert, *Tetrahedron* **1971,** *27,* 2977.

[14] E. Bald, K. Saigo, T. Mukaiyama, *Chem. Lett.* **1975,** 1163.