199. Azomalonic Ester Syntheses

Part I

One-Step Synthesis of Triazolo[1,4]benzodiazepines from Azomalonates. Preparation of Novel Polyaza Tricycles from Diethyl (2-Chloroacetamido)malonate[1])

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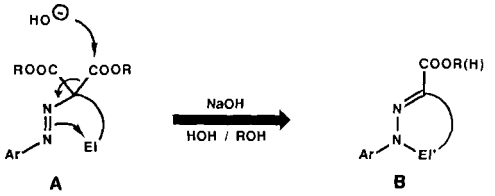
A useful synthetic principle for the preparation of N-heterocycles consists in the base treatment of azomalonates carrying electrophilic centers in the side chain. Thus, pharmacologically active triazolo[1,4]benzodiazepine-carboxamides can be prepared in one step from azomalonates derived from 2-aminobenzophenones and diethyl (2-chloroacetamido)malonate. The same malonate coupled with diazotized 3-amino-2-chloropyridine leads in 2 steps to 3 novel pyridotriazoloazines. Similarly, *N*-protected 2-amino-diphenylamine derivatives are converted into triazoloquinoxaline-carboxylic acids. The heterocycles are further characterized by functional-group interconversion. Some mechanistic aspects of the azomalonic-ester synthesis are discussed.

1. Introduction. – Many fundamentally important chemical reactions have been invented a long time ago. As they come of age, new variations and applications are found, frequently leading to a renaissance in certain synthetic areas. This year marks the 100th anniversary of the *Claisen* condensation, the *Gabriel* synthesis, the *Michael* addition, the *Reformatsky* reaction, the *Willgerodt* reaction as well as the *Japp-Klingemann* reaction [2]. The latter allows the preparation of arylhydrazones of α-ketoesters which are important starting materials in the *Fischer* indole synthesis. We have recently reported [1], in a general way, new applications of the malonic-ester variation of the *Japp-Klingemann* reaction. In this and forthcoming communications, we describe some of our results with experimental details.

2. General Synthetic Principle. – In 1962, *Yao* and *Resnick* [3] presented clear evidence that aromatic-aliphatic azo compounds, the intermediates in the *Japp-Klingemann* reaction, can generally be isolated. One year later, *Regitz* and *Eistert* [4] prepared 1-aryl-5-methyl-1*H*-1,2,4-triazole-3-carboxylic acids directly from stable azo compounds obtained by coupling diethyl(acetamido)malonate with diazonium salts. This represents the first example of the azomalonic-ester synthesis, that is, the one-step conversion of azomalonates into heterocycles according to *Scheme 1*. Azomalonates **A** carrying suitable electrophilic groups (El) on the side chain are treated individually with aqueous base. The reaction is triggered by the attack of OH^- ions on the geminal alkoxycarbonyl

[1]) Presented in part at the XII European Colloquium on Heterocyclic Chemistry, Reims, France, September 1986 [1].

Scheme 1

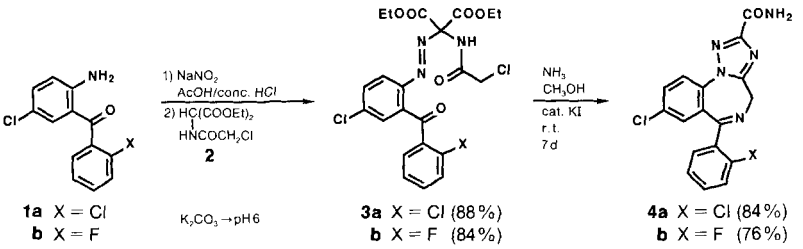


El = *e.g.* COR, COOR, CN, CH(R)Cl, CH=CHCOOR

function. After *Japp-Klingemann* cleavage – a process which, in modern terms, can be regarded as a special case of the *Grob* fragmentation – the nucleophilic aryl-substituted N-atom of the intermediate arylhydrazone interacts directly with the electrophilic center. Depending on the amount of base utilized, this process leads to heterocyclic acids or esters **B**. The functional handle is attractive in medicinal chemistry, since it serves to prepare a variety of derivatives in order to optimize or modify pharmacological activity.

3. Results. – a) *2-Aminobenzophenones as Aromatic Amines.* Using diethyl (2-chloroacetamido)malonate (**2**), we first applied the azomalonic-ester synthesis to the preparation of 1-aryl-5-(chloromethyl)-1*H*-1,2,4-triazole-3-carboxylic acids [5] – valuable precursors for pharmacologically highly active triazolo[1,4]benzodiazepine derivatives [6]. Especially noteworthy in this context is the one-step synthesis of the triazolo[1,4]-benzodiazepine-carboxamides **4** from the crystalline azo compounds **3** *(Scheme 2)*. The

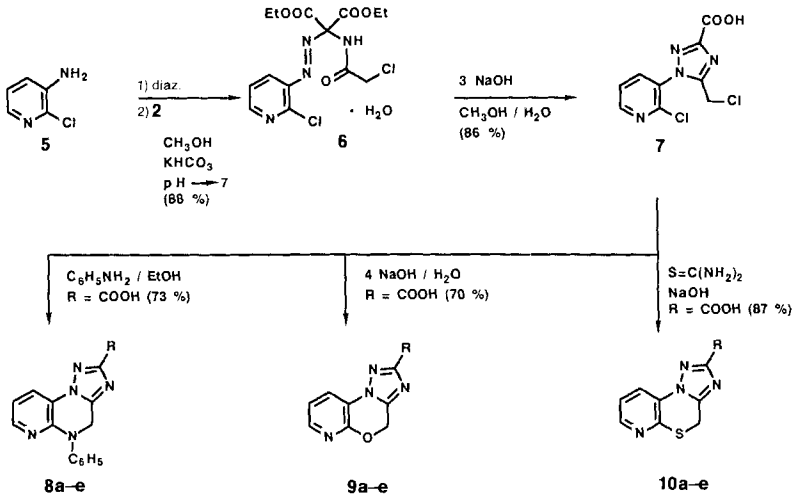
Scheme 2



latter are obtained by coupling diazotized 2-aminobenzophenones **1** with the malonate **2**. Treatment of **3** with NH_3/MeOH at r.t. for 6 days induces the following sequence of events: *Japp-Klingemann* cleavage/triazole-ring closure, ammonolysis of the reactive triazole ester function as well as the chloromethyl group, and finally closure of the 7-membered ring. The carboxamides are isolated by simple filtration. Recrystallization from MeOH gives the analytically pure products **4a** and **4b** in good yields.

b) *3-Amino-2-chloropyridine* (**5**) *as Aromatic Amine (Scheme 3).* Compound **5** with a potential leaving group in *ortho* position to the amine was expected to eventually lead to novel tricycles. After some experimentation, we found that a crystalline monohydrate **6** of the desired azo compound could be prepared by simultaneous addition of a diazonium-salt solution of **5** and saturated aqueous $KHCO_3$ solution to the malonate **2** dissolved in MeOH. Treatment of **6** with 3 equiv. of 1N NaOH for 1 h at r.t. followed by

Scheme 3



a R = COOH; **b** R = H; **c** R = $COOCH_3$; **d** R = $CONH_2$; **e** R = CH_2OH

Table. *Selected Data of the Heterocycles* **8**–**10** *and* **16**[a])

Compound	R	Yield [%][b])	M.p. [°C]	^{1}H-NMR [ppm]	
				ring CH_2	other
8a	COOH	73	205 (sint.), 216–218 (dec.)	5.31[c])	
8b	H	68	175–177	5.32[d])	8.08 (H–C(2))
8c	$COOCH_3$	91	204–206	5.27[d])	4.05 (CH_3O)
8d	$CONH_2$	96	260 (sint.), 284–287 (dec.)	5.30[c])	
8e	CH_2OH	89	237–240	5.26[c])	4.53 (CH_2OH)
9a	COOH	70	213–215 (dec.)	5.80[c])	
9b	H	61	188–190	5.69[d])	8.09 (H–C(2))
9c	$COOCH_3$	91	251–253	5.73[d])	4.07 (CH_3O)
9d	$CONH_2$	97	290 (sint.), 320–323 (dec.)	5.78[c])	
9e	CH_2OH	63	145–147	5.71[c])	4.55 (CH_2OH)
10a	COOH	87	234–237 (dec.)	4.63[c])	
10b	H	63	139–141	4.38[d])	8.08 (H–C(2))
10c	$COOCH_3$	82	243–245	4.67[c])	3.92 (CH_3O)
10d	$CONH_2$	87	250 (sint.), 270–305 (slow dec.)	4.67[c])	
10e	CH_2OH	85	141–144	4.60[c])	4.55 (CH_2OH)
16a	COOH	95	190 (sint.), 205–207 (dec.)	5.11[c])	
16b	H	53	102–105	5.02[d])	8.02 (H–C(2))
16c	$COOCH_3$	83	147–149	5.07[d])	4.06 (CH_3O)
16d	CH_2OH	84	184–188	5.07[c])	4.58 (CH_2OH)

[a]) See *Exper. Part* for complete data.
[b]) Yield of analytically pure products.
[c]) In (D_6)DMSO.
[d]) In $CDCl_3$.

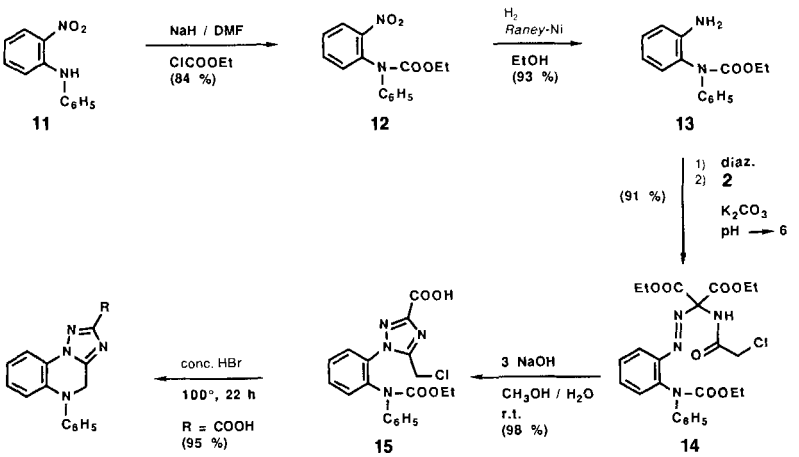
acidification led to the triazolecarboxylic acid **7** which proved to be an ideal precursor for the envisaged heterocycles. Thus, reaction with aniline gave 4,5-dihydro-5-phenylpyrido[2,3-*e*][1,2,4]triazolo[1,5-*a*]pyrazine-2-carboxylic acid (**8a**). Heating of **7** with 4 equiv. of aqueous NaOH solution in the presence of NaI afforded 4*H*-pyrido[2,3-*b*]-[1,2,4]triazolo[1,5-*d*][1,4]oxazine-2-carboxylic acid (**9a**), while the corresponding sulfur-containing heterocycle, 4*H*-pyrido[2,3-*b*][1,2,4]triazolo[1,5-*d*][1,4]thiazine-2-carboxylic acid (**10a**), was produced, when **7** was treated with thiourea in EtOH followed by alkaline hydrolysis. The novel tricycles **8**–**10** were fully characterized by their spectroscopic and analytical data (see *Table*).

In the ^{1}H-NMR spectra, the ring-CH_2 group appears as *s* in the expected order of chemical shift dictated by the electronegativity of the α-heteroatoms, *i.e.* at 4.63 for the thiazine **10a**, 5.31 for the pyrazine **8a**, and 5.80 ppm for the oxazine **9a**. The protons of the pyrido moiety of the heterocycles show up either as *ABX* or as *AMX* systems (see *Exper. Part*). In the latter case, 3 well separated *dd* are observed which, according to first-order treatment, yield the following coupling constants: J(H–C(8), H–C(9)) ≈ 8 Hz, J(H–C(7), H–C(9)) ≈ 1.5 Hz, and J(H–C(7), H–C(8)) ≈ 5 Hz. These values are in good agreement with those published for pyridine derivatives [7].

Decarboxylation of the acids, catalyzed by Cu_2O, provided the parent heterocycles **8b**–**10b**, whereas *Fischer* esterification afforded the methyl esters **8c**–**10c**. Due to the enhanced electrophilic character of alkyl triazolecarboxylates, the corresponding methanol and carboxamide derivatives **8d**–**10d** and **8e**–**10e** could be prepared simply by $NaBH_4$ reduction or ammonolysis, respectively.

c) *Ethyl 2-Amino-*N*-phenylbenzene-1-carbamate* (**13**) *as Aromatic Amine.* Since 2-methaneamine derivatives obtained *via* the mesylate of **8e** showed interesting antidepressant activity in animal screening tests [8], the closely related benzo-annellated tricycles, *i.e.* the [1,2,4]triazolo[1,5-*a*]quinoxalines of type **16** (*Scheme 4*), were also envisaged. For the synthesis of this ring system, we chose *N*-protected *ortho*-phenylenediamine derivatives for the coupling reaction with **2**. The sequence is exemplified for carbamate **13**. The

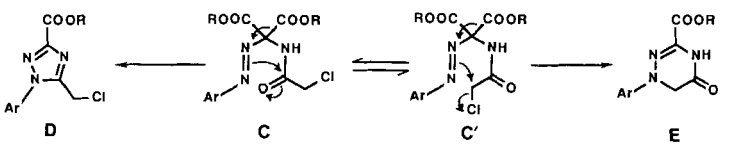
Scheme 4



latter was accessible in 78% overall yield from readily available 2-nitrodiphenylamine (**11**) by ethoxycarbonylation (→**12**) and catalytic reduction of the nitro group. Coupling with **2** gave the crystalline azo compound **14** which was converted to the requisite (chloromethyl)triazolecarboxylic acid **15**. The next step required cleavage of the carbamate function in order to effect ring closure. All experiments in which we used alkaline conditions met with failure. However, the desired tricyclic acid **16a** was formed in high yield upon heating **15** in concentrated aqueous hydrobromic acid at 100°. Fission of the carbamate was expected, but the ready ring closure to the triazoloquinoxaline ring was somewhat surprising. Despite the strongly acidic conditions, a sufficient amount of molecules, unprotonated at the diphenylamine N-atom, must be present to account for the intramolecular nucleophilic displacement of the Cl substituent. The acid **16a** was further characterized by decarboxylation, esterification, and reduction (see *Table*, compounds **16b–d**). The 2-methaneamine derivatives of the alcohol **16d** also showed promising pharmacological activity. Therefore, the same reaction sequence was applied to a variety of substituted derivatives of **13** as well as diethyl 2-[(2-chloropropionyl)-amino]malonate instead of **2** (for details see [8]).

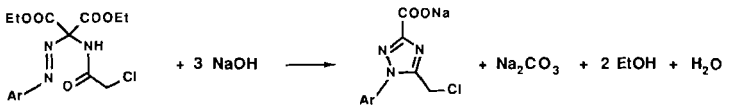
4. Discussion. – The smooth formation of (chloromethyl)triazolecarboxylates from azomalonates deserves the following comments: Azo compounds of type **C** *(Scheme 5)* possess two electrophilic centers in the side chain of the malonates, *i.e.* the amide carbonyl and the chloromethylene group. Thus, in principle and in accordance with the general process (see *Scheme 1*), the nucleophilic aryl N-anion created during the malonic-ester fragmentation, could interact with either one of these electrophilic groups. For the

Scheme 5



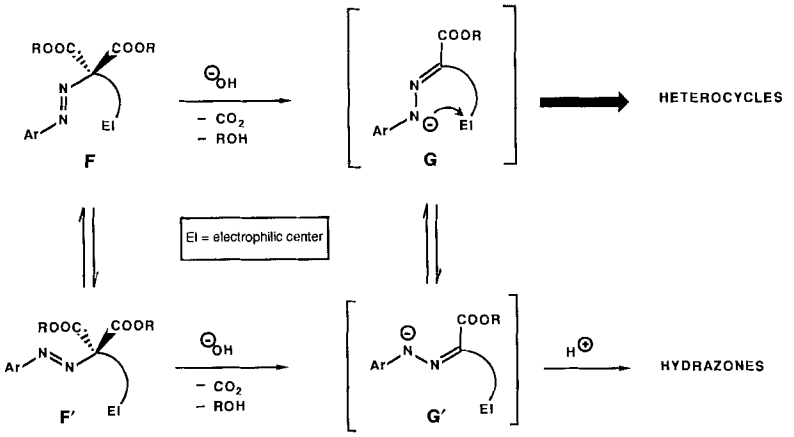
formation of a triazinone of type **E**, rotamer **C'** would be required. While one can hardly explain the favored formation of triazole **D** on the basis of *Baldwin*'s rules for ring closure, *i.e.* by comparing a *6-Exo-Tet* process in the case of **C'**[2]) *vs.* a *5-Exo-Trig* process for **C**[2]), it cannot be ruled out that the observed product **D** is preferred on stereoelectronic grounds. It is important to note that the reaction proceeds at room temperature following the stoichiometry shown in *Scheme 6*. In fact, the best yields of (chloromethyl)triazolecarboxylic acids are obtained with just 3 equiv. of NaOH. A larger

Scheme 6



[2]) The electron arrows denote just the formal course of bond breaking and forming. Most probably, a multistep mechanism may be operative (*cf.* also *Scheme 7* and comments).

Scheme 7



excess of base as well as higher reaction temperatures or prolonged reaction times lead to decreased yields due to the reaction of the chloromethyl group with hydroxide or alkoxide ions.

Another general aspect concerning the azomalonic-ester synthesis is illustrated in *Scheme 7*. In solution, azomalonates are conformationally labile and may exist as a mixture of rotamers **F**/**F'** with the preferred *trans*-configuration of the azo group. Whereas rotamer **F**, after malonic-ester cleavage, yields the intermediate hydrazone anion **G** capable of ring closure, rotamer **F'** leads to the anion **G'** that cannot cyclize for geometric reasons. Thus, in order to rationalize the high yields of cyclized products, one might postulate a rapid isomerization of the anions **G'** and **G**. The latter is removed from the equilibrium by irreversible ring formation. Convincing evidence supporting this view has been presented by *Silverstein* and *Shoolery* [9] who showed that the anions of both geometric forms (*cis* and *trans*) of the 2,4-dinitrophenylhydrazone of ethyl benzoylacetate isomerize rapidly at room temperature with identical rate constants.

In conclusion, we have shown that aryl(chloromethyl)triazolecarboxylic acids – valuable precursors for fused heterocycles – can efficiently be prepared from azo compounds derived from diethyl (2-chloroacetamido)malonate.

I thank *W. Gunzenhauser* and *J. Hunkeler* for skillful experimental assistance. Further thanks are due to Dr. *T. Winkler* and Dr. *H. Hürzeler* for the NMR and the UV spectra, *J. Meier* for the IR spectra, and Dr. *W. Padowetz* for the analytical data. The encouragement and interest of Drs. *H. Allgeier* and *A.R. Gagneux* is gratefully acknowledged.

Experimental Part

General. Unless noted otherwise, reagents and solvents were obtained from commercial sources and used without further purification. TLC: *Merck* precoated plates, silica gel *60* F_{254}; visualization with UV light and/or I_2. Column chromatography (CC): at atmospheric pressure on *Merck* silica gel *60* (70–230 mesh). M.p.: in open capillary tubes on a *Tottoli* apparatus (*Büchi*); uncorrected. pK^* values of acids were determined in 2-methoxyethanol/H_2O 8:2 by titration with 0.1N Me_4NOH. UV spectra (EtOH): *Perkin-Elmer-Lambda-9* spectrometer; λ_{max} (ε) in nm. IR spectra: *Perkin-Elmer-298* spectrometer; absorption bands in cm^{-1}. ^{1}H-NMR spectra: *Varian* (60 and 100 MHz), *Bruker* (250 MHz) spectrometers; δ in ppm relative to internal TMS, coupling constants J in Hz.

Diethyl 2-(2-Chloroacetamido)-2-[4-chloro-2-(2-chlorobenzoyl)phenylazo]malonate (**3a**). To a soln. of 20.0 g (75.2 mmol) of 2-amino-2',5-dichlorobenzophenone (*Aldrich*) in 75 ml of AcOH and 18.8 ml of conc. HCl were added dropwise at 20–25° 15.2 ml (76 mmol) of aq. 5M $NaNO_2$. After the addition, stirring was continued for 15 min at r.t. Then, 55 g of crushed ice was added and a soln. of 18.9 g (75.2 mmol) of diethyl (2-chloroacetamido)malonate (**2**) [10] in 170 ml of acetone was dropped in rapidly. To the resulting well stirred mixture, 115 ml of a sat. aq. K_2CO_3 soln. was added dropwise at 5–10° whereby the pH finally reached 6.5. Stirring was continued at r.t. for 1 h. The mixture was extracted with 2 × 200 ml of AcOEt. The org. extracts were washed with H_2O and brine, dried (Na_2SO_4), and evaporated. The solid residue (41.4 g) was recrystallized from CH_2Cl_2 (40 ml) and hexane (150 ml) to give 35.32 g (89%) of **3a**. M.p. 111–113°. TLC: R_f 0.49 (toluene/AcOEt 6:1). UV: 240 (sh), 289 (11860). IR (CH_2Cl_2): 3400*w* (N–H), 1775*s* (C=O, ester), 1695–1680*s* (C=O, amide and ketone), 1600*w*, 1500*s*, 1355*m*, 1300–1240*s*, 1215*m*, 1195*m*, 1160*m*, 1120*w*, 1100*w*, 1060*w*, 1045*w*, 1015*w*, 946*w*, 860*w*, 835*w*. ^{1}H-NMR (60 MHz, $CDCl_3$): 1.28 (*t*, J = 7, 2 CH_3CH_2O); 3.94 (*s*, CH_2Cl); 4.33 (*q*, J = 7, 2 CH_3CH_2O); 7.25–7.75 (*m*, 7 arom. H, HN). Anal. calc. for $C_{22}H_{20}Cl_3N_3O_6$ (528.78): C 49.97, H 3.81, Cl 20.11, N 7.95; found: C 49.98, H 3.86, Cl 20.09, N 8.16.

Diethyl 2-(2-Chloroacetamido)-2-[4-chloro-2-(2-fluorobenzoyl)phenylazo]malonate (**3b**) was synthesized as described earlier [5] in 85% yield from 2-amino-5-chloro-2'-fluorobenzophenone (*EMKA-Chemie*). UV: 289 with ε = 13800 instead of 138000 as reported in [5].

*8-Chloro-6-(2-chlorophenyl)-4*H*-[1,2,4]triazolo[1,5-a][1,4]benzodiazepine-2-carboxamide* (**4a**). To the suspension of 10.6 g (20.0 mmol) of **3a** and 50 mg of KI in 49 ml of MeOH, 91 ml of *ca.* 5.5M NH_3/MeOH were added. The flask was stoppered and the mixture stirred at r.t. for 7 days (from the initially clear, orange-red soln., slowly bright crystals were deposited). The mixture was evaporated until the final volume was *ca.* 30 ml. The crystals were collected, washed with i-PrOH, and dissolved in 300 ml of hot MeOH and 50 ml of CH_2Cl_2. The clear soln. was evaporated until the volume was 40 ml. After standing overnight at 3°, the crystals were filtered, washed with i-PrOH, and dried at 100°/0.05 Torr for 16 h to give 6.25 g (84%) of **4a**. M.p. 294–300°. TLC: R_f 0.43 (CH_2Cl_2/MeOH 95:5). UV: 219 (sh), 256 (17200), 304 (sh). IR (KBr): 3600–3250*m* (NH_2 ass.), 1720*m*, 1700–1685*s* (C=O, amide), 1630*s* (C=N), 1605*s*, 1535*m*, 1500*m*, 1478*s*, 1442*s*, 1315*m*, 1300*m*, 1275*m*, 1180*m*, 1110*m*, 1065*m*, 1040*m*, 835*s*, 765*m*, 755*s*, 738*s*. ^{1}H-NMR (60 MHz, (D_6)DMSO): 4.88 (*s*, CH_2(4)); 7.21 (*d*, J = 2, H–C(7)); 7.40–8.18 (*m*, 6 arom. H, NH_2). Anal. calc. for $C_{17}H_{11}Cl_2N_5O$ (372.22): C 54.86, H 2.98, Cl 19.05, N 18.82; found: C 54.70, H 2.92, Cl 19.15, N 18.73.

*8-Chloro-6-(2-fluorophenyl)-4*H*-[1,2,4]triazolo[1,5-a][1,4]benzodiazepine-2-carboxamide* (**4b**). In the same way as described above, 10.25 g (20.0 mmol) of **3b** [5] and 50 mg of KI in 49 ml of MeOH were stirred with 91 ml of *ca.* 5.5M NH_3/MeOH for 7 days at r.t. The mixture was evaporated until the final volume was *ca.* 40 ml. After standing overnight at 3°, the crystals were filtered, washed with a small amount of MeOH, and dried at 120°/0.05 Torr for 3 h to give 5.42 g (76%) of **4b**. M.p. 262–265°. TLC: R_f 0.38 (AcOEt/MeOH 95:5). UV: 225 (34160), 254 (sh), 310 (sh). IR (KBr): 3600–3280*m* (NH_2 ass.), 1712*s*, 1700*s* and 1682*s* (C=O, amide), 1628*s* (C=N), 1595*s*, 1543*m*, 1485*s*, 1460*s*, 1440*s*, 1330*m*, 1312*m*, 1265*m*, 1221*s*, 1105*m*, 950*m*, 840*s*, 755*s*. ^{1}H-NMR (60 MHz, (D_6)DMSO): 4.95 (*s*, CH_2(4)); 7.00–8.17 (*m*, 7 arom. H, NH_2). Anal. calc. for $C_{17}H_{11}ClFN_5O$ (355.76): C 57.39, H 3.12, Cl 9.96, F 5.34, N 19.68; found: C 57.49, H 3.00, Cl 10.01, F 5.38, N 19.84.

Diethyl 2-(2-Chloroacetamido)-2-[(2'-chloro-3'-pyridyl)azo]malonate Monohydrate (**6**). To a soln. of 26.0 g (0.202 mol) of 3-amino-2-chloropyridine (*Fluka*) in 200 ml of AcOH and 50 ml of conc. HCl, 40.4 ml (0.202 mol) of aq. 5M $NaNO_2$ were added dropwise at 0–5°. The resulting cold (*ca.* 5°) diazonium-salt soln. was transferred into a dropping funnel and added slowly to a soln. of 40.2 g (0.16 mol) of **2** [10] in 800 ml of MeOH at 15°. Simultaneously, sat. aq. $KHCO_3$ soln. was dropped in at such a rate that the pH of the mixture was maintained at 6. During the addition (*ca.* 40 min), a yellow precipitate appeared. More sat. $KHCO_3$ soln. (total *ca.* 1000 ml) was added until the pH reached 7. Stirring was continued at r.t. for 2 h. After standing overnight at r.t., the crystals were collected, washed copiously with H_2O and hexane, and dried for 7 days at r.t. in the *open air* to give 57.7 g (88%) of **6**. M.p. 61° (sint.), 66–68°. TLC: R_f 0.48 (toluene/AcOEt 3:2). UV: 218 (12500), 255 (sh), 298 (6200). IR (CH_2Cl_2): 3700*w*

(H_2O), 3403*m* (NH), 3070*w*, 3000*w*, 1760*s* (C=O, ester), 1705*s* (C=O, amide), 1582*m*, 1510*s*, 1419*s*, 1380*m*, 1310–1260*s*, 1224*s*, 1192*s*, 1090*m*, 1020*m*, 865*w*, 816*w*. ^{1}H-NMR (60 MHz, $CDCl_3$): 1.35 (*t*, *J* = 7, 2 CH_3CH_2O); 1.85 (br. *s*, 1 H of H_2O), 4.17 (*s*, CH_2Cl); 4.43 (*q*, *J* = 7, 2 CH_3CH_2O); 7.33 (*dd*, *J* = 4.4, 8, H–C(5')); 7.91 (*dd*, *J* = 1.5, 8, H–C(4')); 8.10 (br. *s*, NH); 8.75 (*dd*, *J* = 1.5, 4.4, H–C(6')). Anal. calc. for $C_{14}H_{16}Cl_2N_4O_5 \cdot H_2O$ (409.23): C 41.09, H 4.43, Cl 17.33, N 13.68, H_2O 4.40; found: C 41.1, H 4.5, Cl 17.3, N 13.7, H_2O 4.5.

*1-(2'-Chloro-3'-pyridyl)-5-(chloromethyl)-1*H*-1,2,4-triazole-3-carboxylic Acid* (**7**). A cold (2°) soln. of 37.0 g (90.4 mmol) of **6** in 370 ml of MeOH was added in 1 portion to 271 ml (271 mmol) of well stirred 1N NaOH precooled to 2°. The temp. of the mixture reached 20° despite external cooling with ice/H_2O. When the exothermic reaction subsided, stirring was continued at r.t. for 70 min, 10 g of decolorising charcoal was added, and after stirring for 10 min at r.t., the mixture was filtered through a *Celite* pad which was washed with H_2O (50 ml). The pH of the clear yellow filtrate was adjusted to 3 by slow addition of 2N HCl (*ca.* 132 ml). After stirring for 90 min at 0°, the crystals were collected, washed copiously with H_2O, Et_2O, and hexane, and dried at 100°/0.05 Torr for 3 h to give 21.25 g (86%) of **7**. M.p. 211–214° (dec.). TLC: R_f 0.30 (CH_2Cl_2/MeOH 1:1). p*K** = 4.70 (equiv. mol. weight: 271). UV: 210 (sh), 266 (3860), 272 (sh). IR (KBr): 3600–3320*m* (OH ass.), 3105*m*, 3060*m*, 3000–2300*m*, 1750*s* (C=O, acid), 1600*m*, 1580*s*, 1525*m*, 1505*s*, 1472*s*, 1448*s*, 1420*m*, 1388*m*, 1240*m*, 1220*s*, 1180*s*, 1148*m*, 1140*m*, 1045*s*, 955*m*, 836*s*, 805*m*, 770*s*, 739*s*, 721*s*, 670*m*, 653*s*. ^{1}H-NMR (60 MHz, (D_6)DMSO): 4.87 (*s*, CH_2Cl); 7.70 (*dd*, *J* = 4.6, 8, H–C(5')); 8.34 (*dd*, *J* = 1.5, 8, H–C(4')); 8.70 (*dd*, *J* = 1.5, 4.6, H–C(6')); 13.5 (very br., COOH). Anal. calc. for $C_9H_6Cl_2N_4O_2$ (273.08): C 39.59, H 2.22, Cl 25.97, N 20.52; found: C 39.76, H 2.38, Cl 25.52, N 20.35.

*4,5-Dihydro-5-phenylpyrido[2,3-*e*][1,2,4]triazolo[1,5-*a*]pyrazine-2-carboxylic Acid* (**8a**). A mixture of 14.20 g (52 mmol) of **7**, 0.20 g of KI, and 19.37 ml (19.75 g, 212 mmol) of aniline in 450 ml of EtOH was stirred at reflux for 64 h. The soln. was evaporated and the residue dissolved at 50° in 250 ml of H_2O and 150 ml of 1N NaOH. After cooling to r.t., the soln. was extracted thrice with 50 ml of Et_2O. The org. extracts were washed with 50 ml of 0.1N NaOH. To the stirred combined aq. layers, 5N HCl was added until the pH of the mixture reached 2.5. After standing overnight at 0°, the colorless crystals were filtered, washed copiously with H_2O, and dried at 110°/0.05 Torr for 3 h to give 11.13 g (73%) of **8a**. M.p. 205° (sint.), 216–218° (dec.). TLC: R_f 0.45 (longish spot, CH_2Cl_2/MeOH 1:1). p*K** = 4.63 (equiv. mol. weight: 294). UV: 221 (19500), 290 (9200), 340 (7400). IR (nujol): 3350–2700*m* (OH ass.), 1760*s* (C=O, acid), 1635*m*, 1615*m*, 1545*m*, 1510*s*, 1375*s*, 1290*m*, 1275*m*, 1255*m*, 1203*s*, 1105*m*, 1060*w*, 760*m*, 750*s*, 736*m*, 694*s*. ^{1}H-NMR (60 MHz, (D_6)DMSO): 5.31 (*s*, CH_2(4)); 6.90 (*dd*, *X* of *ABX*, H–C(8)); 7.25–7.55 (*m*, C_6H_5); 7.83–8.08 (*m*, *AB* of *ABX*, H–C(7), H–C(9)); 13.2 (very br., COOH). Anal. calc. for $C_{15}H_{11}N_5O_2$ (293.29): C 61.43, H 3.78, N 23.88; found: C 61.5, H 4.0, N 23.9.

*4*H*-Pyrido[2,3-*b*][1,2,4]triazolo[1,5-*d*][1,4]oxazine-2-carboxylic Acid* (**9a**). A mixture of 12.30 g (45 mmol) of **7**, 6.75 g (45 mmol) of NaI in 180 ml (180 mmol) of 1N NaOH and 400 ml of H_2O was stirred at r.t. for 3 h and then at 90° for 2.5 h. After cooling to *ca.* 40°, the soln. was filtered through a plug of cotton wool and acidified by the addition of 5N HCl (*ca.* 18 ml, final pH 2.5). The mixture was kept at 0° for 16 h, and the crystals were filtered and washed with H_2O and Et_2O. The crude product (7.90 g) was dissolved in 40 ml of 1N NaOH, 130 ml of H_2O, and 130 ml of MeOH. The stirred clear soln. was warmed to 50°, and 41 ml of 1N HCl were added (final pH 2.5). After stirring for 2 h at 0°, the crystals were collected, washed with H_2O and Et_2O, and dried at 120°/0.05 Torr for 3 h to give 6.86 g (70%) of **9a**. M.p. 213–215° (dec.). TLC: R_f 0.4 (tailing spot, MeOH/AcOH 95:5). p*K** = 4.52 (equiv. mol. weight: 222). UV: 210 (sh), 252 (6000), 263 (5500), 293 (13000). IR (nujol): 3400–2300*m* (OH ass.), 1720*s* (C=O, acid), 1610*m*, 1528*m*, 1373*m*, 1350*m*, 1240–1210*s*, 1115*w*, 1050*m*, 1005*m*, 848*w*, 805*m*, 765*m*, 748*m*, 700*w*. ^{1}H-NMR (100 MHz, (D_6)DMSO): 5.80 (*s*, CH_2(4)); 7.26 (*dd*, *X* of *ABX*, H–C(8)); 8.09–8.23 (*m*, *AB* of *ABX*, H–C(7), H–C(9)); COOH not visible. Anal. calc. for $C_9H_6N_4O_3$ (218.17): C 49.55, H 2.77, N 25.68; found: C 49.4, H 2.9, N 25.4.

*4*H*-Pyrido[2,3-*b*][1,2,4]triazolo[1,5-*d*][1,4]thiazine-2-carboxylic Acid* (**10a**). A soln. of 25.0 g (91.5 mmol) of **7** and 7.7 g (101 mmol) of thiourea in 500 ml of EtOH was heated at reflux for 5 h. The mixture was evaporated and the amorphous yellow residue (41.3 g, thiuronium salt) treated under N_2 with a soln. of 18.3 g (457 mmol) of NaOH in 230 ml of H_2O. The mixture was heated at reflux for 2 h. After cooling to r.t., the crystalline sodium salt was filtered, washed with brine, and suspended in 180 ml of H_2O. Then, 2N HCl was added until the pH reached 2.5. After stirring overnight at r.t., the crystals were filtered, washed with H_2O and Et_2O and dried at 100°/0.05 Torr for 5 h to give 18.8 g (88%) of **10a**. M.p. 234–237° (dec.). TLC: R_f 0.37 (longish spot, MeOH/AcOH 95:5). p*K** = 4.63 (equiv. mol. weight: 238). UV: 240 (5980), 286 (2500), 307 (2720). IR (nujol): 3400–2300*w* (OH ass.), 1720*s* (C=O, acid), 1590*m*, 1518*m*, 1500*m*, 1465*s*, 1420*s*, 1380*s*, 1360*s*, 1235*s*, 1225*s*, 1110*m*, 1034*m*, 815*m*, 808*m*, 797*m*, 765*m*, 750*m*, 740*m*, 725*m*, 673*m*. ^{1}H-NMR (100 MHz, (D_6)DMSO): 4.63 (*s*, CH_2(4)); 7.45 (*dd*, *J* = 5, 8, H–C(8)); 8.18 (*dd*, *J* = 1.5, 8, H–C(9)); 8.45 (*dd*, *J* = 1.5, 5, H–C(7)); 12.2–13.8 (very br., COOH). Anal. calc. for $C_9H_6N_4O_2S$ (234.23): C 46.15, H 2.59, N 23.92, S 13.69; found: C 46.1, H 2.7, N 23.7, S 13.4.

Decarboxylation of **8a–10a**. *General Procedure*. The acid was dissolved at 120° in 2,2'-oxydiethanol (= diethylene glycol). A cat. amount of Cu_2O was added and the mixture stirred at 135° (bath temp. *ca.* 145°) for 7 h (cessation of CO_2 evolution). The mixture was poured into ice/H_2O and extracted with AcOEt. The extracts were washed with sat. $KHCO_3$ soln., H_2O and brine, dried ($MgSO_4$), and evaporated to give the crude products.

*4,5-Dihydro-5-phenylpyrido[2,3-*e*][1,2,4]triazolo[1,5-*a*]pyrazine* (**8b**). From 4.0 g (13.6 mmol) of **8a** and 40 mg of Cu_2O in 80 ml of 2,2'-oxydiethanol, 3.3 g of crude **8b** were obtained. Crystallization from CH_2Cl_2/i-PrOH gave 2.33 g (69%). M.p. 175–177°. TLC: R_f 0.67 (AcOEt). UV: 219 (21000), 290 (9000), 328 (7020). IR (CH_2Cl_2): 1630*m*, 1605*m*, 1587*w*, 1545*m*, 1510*s*, 1480*s*, 1450*s*, 1390*m*, 1300–1250*m*, 1175*m*, 1100*m*. ^{1}H-NMR (60 MHz, $CDCl_3$): 5.32 (*s*, CH_2(4)); 6.83 (*dd*, *X* of *ABX*, H–C(8)); 7.25–7.60 (*m*, C_6H_5); 7.88–8.18 (*m*, *AB* of *ABX*, H–C(7)); 8.08 (*s*, H–C(2)). Anal. calc. for $C_{14}H_{11}N_5$ (249.28): C 67.46, H 4.45, N 28.09; found: C 67.09, H 4.62, N 27.84.

*4*H*-Pyrido[2,3-*b*][1,2,4]triazolo[1,5-*d*][1,4]oxazine* (**9b**). From 4.0 g (18.3 mmol) of **9a** and 40 mg of Cu_2O in 80 ml of 2,2'-oxydiethanol, 2.32 g of crude **9b** were obtained. CC on 120 g of silica gel with CH_2Cl_2/MeOH 98:2 followed by crystallization from CH_2Cl_2/i-PrOH gave 1.94 g (61%) of **9b**. M.p. 188–190°. TLC: R_f 0.46 (CH_2Cl_2/MeOH 95:5). UV: 204 (18660), 250 (4380), 291 (10380). IR (CH_2Cl_2): 1620*m*, 1603*m*, 1541*s*, 1508*s*, 1471*s*, 1451*s*, 1376*m*, 1248*m*, 1226*m*, 1170*s*, 1076*m*, 1049*s*, 1019*m*, 843*m*, 802*m*. ^{1}H-NMR (250 MHz, $CDCl_3$): 5.69 (*s*, CH_2(4)); 7.15 (*dd*, J = 5, 8, H–C(8)); 8.06 (*dd*, J = 1.5, 8, H–C(9)); 8.09 (*s*, H–C(2)); 8.16 (*dd*, J = 1.5, 5, H–C(7)). Anal. calc. for $C_8H_6N_4O$ (174.16): C 55.17, H 3.47, N 32.17; found: C 55.11, H 3.59, N 31.88.

*4*H*-Pyrido[2,3-*b*][1,2,4]triazolo[1,5-*d*][1,4]thiazine* (**10b**). From 7.0 g (29.9 mmol) of **10a** and 70 mg of Cu_2O in 140 ml of 2,2'-oxydiethanol, 4.6 g of crude **10b** were obtained. CC on 460 g of silica gel with CH_2Cl_2/MeOH 95:5 followed by crystallization from CH_2Cl_2/i-PrOH gave 3.6 g (63%) of **19b**. M.p. 139–141°. TLC: R_f 0.57 (CH_2Cl_2/MeOH 95:5). UV: 228 (sh), 234 (14200), 282 (sh), 302 (5600). IR (CH_2Cl_2): 1585*m*, 1530*s*, 1485*s*, 1442*m*, 1420*s*, 1365*s*, 1235*m*, 1170*s*, 1140*m*, 1082*s*, 1015*m*, 890*m*, 802*s*. ^{1}H-NMR (60 MHz, $CDCl_3$): 4.38 (*s*, CH_2(4)); 7.23 (*dd*, J = 5, 8, H–C(8)); 8.08 (*s*, H–C(2)); 8.10 (*dd*, J = 1.5, 8, H–C(9)); 8.19 (*dd*, J = 1.5, 5, H–C(7)). Anal. calc. for $C_8H_6N_4S$ (190.22): C 50.52, H 3.18, N 29.46, S 16.86; found: C 50.5, H 3.2, N 29.5, S 16.9.

Esterification of **8a–10a**. *General Procedure*. A suspension of the acid in MeOH containing HCl was stirred at reflux for 17 h. The mixture was evaporated and the residue taken up in CH_2Cl_2, ice-water and sat. $KHCO_3$ soln. The extracts were washed with sat. $KHCO_3$ soln. and brine, dried ($MgSO_4$), and evaporated to give the crude esters.

*Methyl 4,5-Dihydro-5-phenylpyrido[2,3-*e*][1,2,4]triazolo[1,5-*a*]pyrazine-2-carboxylate* (**8c**). From 5.86 g (20 mmol) of **8a** in 80 ml of MeOH and 15 ml of *ca.* 6M HCl/MeOH, 5.9 g of crude **8c** were obtained. Two recrystallizations from CH_2Cl_2/i-PrOH gave 5.64 g (92%). M.p. 204–206°. TLC: R_f 0.66 (AcOEt). UV: 222 (18600), 289 (8800), 342 (7400). IR (CH_2Cl_2): 1720*s* (C=O, ester), 1620*m*, 1605*m*, 1500*s*, 1470*s*, 1450*s*, 1215*s* (O–C, ester), 1180*m*, 1158*m*, 1110*m*, 1015*w*, 960*w*, 828*w*. ^{1}H-NMR (60 MHz, $CDCl_3$): 4.05 (*s*, CH_3O); 5.27 (*s*, CH_2(4)); 6.87 (*dd*, *X* of *ABX*, H–C(8)); 7.25–7.55 (*m*, C_6H_5); 8.00–8.23 (*m*, *AB* of *ABX*, H–C(7), H–C(9)). Anal. calc. for $C_{16}H_{13}N_5O_2$ (307.31): C 62.54, H 4.27, N 22.79; found: C 62.25, H 4.38, N 22.67.

*Methyl 4*H*-Pyrido[2,3-*b*][1,2,4]triazolo[1,5-*d*][1,4]oxazine-2-carboxylate* (**9c**). From 3.0 g (13.7 mmol) of **9a** in 60 ml of MeOH and 12 ml of *ca.* 6M HCl/MeOH, 3.15 g of crude **9c** were obtained. Crystallization from CH_2Cl_2/i-PrOH gave 2.92 g (91%). M.p. 251–253°. TLC: R_f 0.37 (CH_2Cl_2/MeOH 95:5). UV: 201 (14000), 210 (13300), 253 (5600), 263 (sh), 297 (12400). IR (nujol): 1748*s* (C=O, ester), 1620*w*, 1600*w*, 1545*w*, 1503*m*, 1380*m*, 1255*m*, 1220*s* (O–C, ester), 1185*s*, 1160*m*, 1120*m*, 1072*m*, 1050*m*, 1010*m*, 955*w*, 850*m*, 820*m*, 780*w*, 755*w*. ^{1}H-NMR (100 MHz, $CDCl_3$): 4.07 (*s*, CH_3O); 5.73 (*s*, CH_2(4)); 7.20 (*dd*, *X* of *ABX*, H–C(8)); 8.15–8.30 (*m*, *AB* of *ABX*, H–C(7), H–C(9)). Anal. calc. for $C_{10}H_8N_4O_3$ (232.20): C 51.73, H 3.48, N 24.13; found: C 51.67, H 3.51, N 23.88.

*Methyl 4*H*-Pyrido[2,3-*b*][1,2,4]triazolo[1,5-*d*][1,4]thiazine-2-carboxylate* (**10c**). From 11.5 g (49.1 mmol) of **10a** in 115 ml of MeOH and 23 ml of *ca.* 6M HCl/MeOH, 11.1 g of crude **10c** were obtained. Crystallization from CH_2Cl_2/i-PrOH gave 10.0 g (82%) of **10c**. M.p. 243–245°. TLC: R_f 0.5 (CH_2Cl_2/MeOH 95:5). UV: 225 (sh), 241 (13400), 284 (5600), 309 (6800). IR (nujol): 1750*s* (C=O, ester), 1530*m*, 1370*s*, 1290*m*, 1220*s* (O–C, ester), 1165*m*, 1103*m*, 1008*m*, 955*m*, 834*m*, 800*m*, 782*m*, 730*m*. ^{1}H-NMR (100 MHz, (D_6)DMSO): 3.92 (*s*, CH_3O); 4.67 (*s*, CH_2(4)); 7.45 (*dd*, J = 5, 8.4, H–C(8)); 8.20 (*dd*, J = 1.5, 8.4, H–C(9)); 8.45 (*dd*, J = 1.5, 5, H–C(7)). Anal. calc. for $C_{10}H_8N_4O_2S$ (248.26): C 48.38, H 3.25, N 22.57, S 12.91; found: C 48.37, H 3.33, N 22.50, S 12.65.

Ammonolysis of **8c–10c**. *General Procedure*. A suspension of the ester in *ca.* 5.5M NH_3/MeOH was stirred at r.t. in a closed vessel for 2 days. The mixture was cooled and the crystalline product filtered, washed with MeOH and Et_2O and dried at 120°/0.05 Torr for 3 h to give the anal. pure carboxamide.

*4,5-Dihydro-5-phenylpyrido[2,3-*e*][1,2,4]triazolo[1,5-*a*]pyrazine-2-carboxamide* (**8d**). From 3.07 g (10 mmol) of **8c** in 60 ml of *ca.* 5.5M NH_3/MeOH, 2.82 g (96%) of **8d** were obtained. M.p. 260° (sint.), 284–287° (dec.). TLC: R_f 0.34 (AcOEt). UV: 222 (20900), 290 (9270), 339 (7820). IR (nujol): 3470*m* and 3170*m* (br., NH, NH ass.),

1720*s* and 1690*m* (C=O, amide), 1610*m*, 1515*s*, 1380*s*, 1300*s*, 1270*s*, 1105*m*, 752*s*, 692*m*. ^{1}H-NMR (250 MHz, (D_6)DMSO): 5.30 (*s*, $CH_2(4)$); 6.95 (*dd*, *X* of *ABX*, H–C(8)); 7.27 (*m*, H_p of C_6H_5); 7.37–7.50 (*m*, 2 H_o and 2 H_m of C_6H_5); 7.75 (br. *s*, NH); 7.92–8.00 (*m*, *AB* of *ABX*, H–C(7), H–C(9)); 8.03 (br. *s*, NH). Anal. calc. for $C_{15}H_{12}N_6O$ (292.30): C 61.64, H 4.14, N 28.75; found: C 61.51, H 4.14, N 28.67.

4H-Pyrido[2,3-b][1,2,4]triazolo[1,5-d][1,4]oxazine-2-carboxamide (**9d**). From 638 mg (2.75 mmol) of **8c** in 30 ml of *ca.* 4.5M NH_3/MeOH, 579 mg (97%) of **9d** were obtained. M.p. 290° (sint.), 320–323° (dec.). TLC: R_f 0.42 (CH_2Cl_2/MeOH 9:1). UV: 211 (3850), 253 (1480), 296 (3230). IR (nujol): 3420*m*, 3390*m*, 3330*m*, 3250*m* and 3180*m* (NH, NH ass.), 1705*s* and 1693*s* (C=O, amide), 1612*m*, 1482*m*, 1375*m*, 1274*m*, 1252*m*, 1052*m*, 830*m*. ^{1}H-NMR (250 MHz, (D_6)DMSO): 5.78 (*s*, $CH_2(4)$); 7.25 (*dd*, J = 5, 7.5, H–C(8)); 7.77 (br. *s*, NH); 8.01 (br. *s*, NH); 8.08 (*dd*, J = 1, 7.5, H–C(9)); 8.15 (*dd*, J = 1, 5, H–C(7)). Anal. calc. for $C_9H_7N_5O_2$ (217.19): C 49.77, H 3.25, N 32.25; found: C 49.83, H 3.30, N 32.02.

4H-Pyrido[2,3-b][1,2,4]triazolo[1,5-d][1,4]thiazine-2-carboxamide (**10d**). From 9.5 g (38.7 mmol) of **10c** in 230 ml of *ca.* 5.5M NH_3/MeOH, 7.85 g (87%) of **10d** were obtained. M.p. 250° (sint.), 270–305° (slow dec.). TLC: R_f 0.27 (CH_2Cl_2/MeOH 95:5). UV: 240 (14500), 286 (5740), 307 (6340). IR (nujol): 3400*m* (NH), 3300*w*–3140*m* (NH ass.), 1705*s* (C=O, amide), 1612*w*, 1580*w*, 1510*m*, 1412*m*, 1370*m*, 1305*m*, 1270*m*, 1235*w*, 1025*w*, 805*m*, 793*m*, 734*m*. ^{1}H-NMR (250 MHz, (D_6)DMSO): 4.67 (*s*, $CH_2(4)$); 7.45 (*dd*, J = 5, 8.5, H–C(8)); 7.78 (br. *s*, NH); 8.05 (br. *s*, NH); 8.15 (*dd*, J = 1.5, 8.5, H–C(9)); 8.45 (*dd*, J = 1.5, 5, H–C(7)). Anal. calc. for $C_9H_7N_5OS$ (233.25): C 46.35, H 3.03, N 30.03, S 13.75; found: C 46.0, H 3.2, N 29.5, S 13.7.

Reduction of **8c**–**10c**. *General Procedure.* A suspension of the ester in MeOH/THF 1:1 was treated with an excess of $NaBH_4$ at r.t. After the transitory exothermic reaction (35–40° max.), the mixture was stirred at r.t. for 90 min. Workup was somewhat different in each case.

4,5-Dihydro-5-phenylpyrido[2,3-e][1,2,4]triazolo[1,5-a]pyrazine-2-methanol (**8e**). A soln. of 18.6 g (60.6 mmol) of **8c** in 1200 ml of MeOH/THF 1:1 was reduced with 11.4 g (303 mmol) of $NaBH_4$. The mixture was diluted with 600 ml of H_2O. After stirring at 0° for 2 h, the crystals were filtered, washed copiously with H_2O, and dried at 100°/0.05 Torr for 6 h to give 15.1 g (89%) of **8e**. M.p. 237–240°. TLC: R_f 0.39 (CH_2Cl_2/MeOH 95:5). UV: 207 (20470), 222 (20380), 293 (8910), 328 (7500). IR (nujol): 3220*m* (br., OH ass.), 1635*w*, 1540*m*, 1380*m*, 1285*m*, 1270*m*, 1110*w*, 1070*m*, 1060*m*, 1020*w*, 786*m*, 780*m*, 750*m*, 703*m*. ^{1}H-NMR (250 MHz, (D_6)DMSO): 4.53 (*d*, J = 6, becomes *s* after exchange with D_2O, CH_2OH); 5.26 (*s*, $CH_2(4)$); 5.47 (*t*, J = 6, exchangeable with D_2O, OH); 6.90 (*dd*, *X* of *ABX*, H–C(8)); 7.23 (*m*, H_p of C_6H_5); 7.35–7.50 (*m*, 2 H_o and 2 H_m of C_6H_5); 8.85–8.94 (*m*, *AB* of *ABX*, H–C(7), H–C(9)). Anal. calc. for $C_{15}H_{13}N_5O$ (279.30): C 64.51, H 4.69, N 25.08; found: C 64.41, H 4.67, N 25.03.

4H-Pyrido[2,3-b][1,2,4]triazolo[1,5-d][1,4]oxazine-2-methanol (**9e**). A soln. of 1.5 g (6.46 mmol) of **9c** in 130 ml of MeOH/THF 1:1 was reduced with 1.22 g (32.3 mmol) of $NaBH_4$. The mixture was diluted with 50 ml of H_2O and evaporated. The residue was dissolved in 0.5N HCl and stirred for 30 min. Then, 2N NaOH was added until the pH reached 9, and the mixture was saturated with NaCl and extracted with AcOEt. The org. extracts were washed with brine, dried (Na_2SO_4), and evaporated to give 1.09 g of crude **9e**. Crystallization from i-PrOH afforded 0.83 g (63%). M.p. 145–147°. TLC: R_f 0.22 (CH_2Cl_2/MeOH 95:5). UV: 205 (18050), 251 (4750), 293 (11340). IR (nujol): 3340–3150*m* (OH ass.), 1610*w*, 1535*s*, 1512*m*, 1370*m*, 1260*w*, 1242*m*, 1220*m*, 1080*m*, 1070*m*, 1048*s*, 1002*m*, 845*w*, 815*w*, 805*w*. ^{1}H-NMR (100 MHz, (D_6)DMSO): 4.55 (*d*, J = 6.4, becomes *s* after exchange with D_2O, CH_2OH); 5.47 (*t*, J = 6.4, exchangeable with D_2O, OH); 5.71 (*s*, $CH_2(4)$); 7.21 (*dd*, *X* of *ABX*, H–C(8)); 7.29–8.14 (*m*, *AB* of *ABX*, H–C(7), H–C(9)). Anal. calc. for $C_9H_8N_4O_2$ (204.19): C 52.94, H 3.95, N 27.44; found: C 53.00, H 3.95, N 27.50.

4H-Pyrido[2,3-b][1,2,4]triazolo[1,5-d][1,4]thiazine-2-methanol (**10e**). A soln. of 10.0 g (40.3 mmol) of **10c** in 800 ml of MeOH/THF 1:1 was reduced with 7.63 g (201 mmol) of $NaBH_4$. The mixture was diluted with 100 ml of H_2O and evaporated. The residue was taken up in H_2O and CH_2Cl_2, and the pH was adjusted to 9 by the addition of AcOH. The org. extracts were washed with brine, dried (Na_2SO_4), and evaporated to give 8.6 g of crude **10e**. Crystallization from i-PrOH afforded 7.6 g (86%) of **10e**. M.p. 141–144°. TLC: R_f 0.29 (CH_2Cl_2/MeOH 95:5). UV: 238 (14700), 302 (6400). IR (nujol): 3300–3150*m* (OH ass.), 1585*w*, 1540*m*, 1425*s*, 1370*m*, 1352*m*, 1048*s*, 1030*m*, 1015*w*, 813*m*, 731*m*. ^{1}H-NMR (60 MHz, (D_6)DMSO): 4.55 (*d*, J = 6, becomes *s* after exchange with D_2O, CH_2OH); 4.60 (*s*, $CH_2(4)$); 5.43 (*t*, J = 6, exchangeable with D_2O, OH); 7.39 (*dd*, J = 5, 8, H–C(8)); 8.05 (*dd*, J = 1.5, 8, H–C(9)); 8.37 (*dd*, J = 1.5, 5, H–C(7)). Anal. calc. for $C_9H_8N_4OS$ (220.25): C 49.08, H 3.66, N 25.44, S 14.56; found: C 49.30, H 3.63, N 25.46, S 14.26.

Ethyl 2-Nitro-N-phenylbenzene-1-carbamate (**12**). A soln. of 14.14 g (66 mmol) of 2-nitrodiphenylamine (**11**; *Aldrich*) in 90 ml of DMF was added dropwise at 10–15° under N_2 to a suspension of 3.17 g (*ca.* 72 mmol) of NaH (*ca.* 55% in mineral oil) in 18 ml of DMF. Stirring was continued at r.t. for 3 h. Then, 7.5 ml (8.53 g, 78.6 mmol) of ethyl chloroformate was added. The dark violet color of the mixture changed to yellow-orange and the pH reached 8. After having been stirred for 30 min at r.t., the mixture was cooled to 5°, and AcOH was added dropwise until the

pH reached 4. Then, 220 ml of ice-water and 200 ml of AcOEt were added. The org. extracts were washed with H_2O and brine, dried (Na_2SO_4), and evaporated. The residual oil was treated with 35 ml of hexane and 18 ml of H_2O and stirred at r.t. for 17 h. The orange crystals that had formed were collected, washed with H_2O and hexane, and recrystallized from i-PrOH to give 16.04 g (85%) of **12**. M.p. 56–58°. TLC: R_f 0.44 (toluene/AcOEt 9:1). UV: 234 (17000), 326 (1600). IR (CH_2Cl_2): 1735*s* (C=O, ester), 1615*m*, 1600*m*, 1540*s* (NO_2), 1495*m*, 1395*m*, 1370*s*, 1352*s* (NO_2), 1310*s*, 1220*m*, 1095*w*, 1065*m*, 1040*w*, 1030*w*, 848*w*. ^{1}H-NMR (60 MHz, $CDCl_3$): 1.12 (*t*, *J* = 7.5, CH_3CH_2O); 4.15 (*q*, *J* = 7.5, CH_3CH_2O); 7.05–7.58 (*m*, 8 arom. H); 7.95 (*m*, H_o to NO_2). Anal. calc. for $C_{15}H_{14}N_2O_4$ (286.29): C 62.93, H 4.93, N 9.79; found: C 63.03, H 4.95, N 10.04.

*Ethyl 2-Amino-*N*-phenylbenzene-1-carbamate* (**13**). A soln. of 35.15 g (122.8 mmol) of **12** in 350 ml of EtOH was hydrogenated at ordinary pressure in the presence of 10.5 g of *Raney* Ni for 29 h at 15–20°. The catalyst was filtered off through a *Celite* pad, and the filtrate was evaporated. The crude product (32 g) was recrystallized from CH_2Cl_2/hexane to give 29.2 g (93%) of **13**. M.p. 87–90°. TLC: R_f 0.68 (toluene/AcOEt 6:4). UV: 228 (18060), 293 (3160). IR (CH_2Cl_2): 3470*w* and 3385*w* (NH_2), 1710*s* (C=O, ester), 1620*s*, 1600*m*, 1495*s*, 1455*m*, 1395*m*, 1370*s*, 1305*s*, 1215*s*, 1155*w*, 1095*m*, 1060*s*, 1030*m*. ^{1}H-NMR (60 MHz, $CDCl_3$): 1.20 (*t*, *J* = 7, CH_3CH_2O); 3.72 (br. *s*, exchangeable with D_2O, NH_2); 4.19 (*q*, *J* = 7, CH_3CH_2O); 6.50–7.32 (*m*, 9 arom. H). Anal. calc. for $C_{15}H_{16}N_2O_2$ (256.31): C 70.29, H 6.29, N 10.93; found: C 70.47, H 6.59, N 11.14.

*Diethyl 2-{2-Chloroacetamido}-2-{[2-(*N*-ethoxycarbonyl-*N*-phenylamino)phenyl]azo}malonate* (**14**). To a soln. of 79.4 g (0.31 mol) of **13** in 744 ml of AcOH and 186 ml of conc. HCl, 62 ml (0.31 mol) of aq. 5M $NaNO_2$ were added dropwise at 2–5° within 30 min. After the addition, stirring was continued for 15 min at 2°. Then, 185 g of crushed ice were added, and a soln. of 77.8 g (0.31 mol) of **2** [10] in 778 ml of acetone was dropped in rapidly. To the resulting well stirred suspension, 1430 ml of a sat. K_2CO_3 soln. was added slowly at 5° within 1 h (pH *ca.* 6). Stirring was continued at 5° for 1 h. Then, 2000 ml of ice-water and 70 ml of Et_2O were added. After stirring for 1 h at 5°, the yellow crystals were filtered, washed copiously with H_2O and 4 portions (400 ml each) of Et_2O. The product was dried over $CaCl_2$ for 2 days. Thus, 146.6 g (91%) of **14** were obtained. M.p. 102–104°. TLC: R_f 0.5 (toluene/AcOEt 3:1). UV: 227 (17400), 276 (9200), 330 (sh). IR (CH_2Cl_2): 3400*w* (NH), 1750*s* (C=O, malonate), 1720–1695*s* (C=O, carbamate and amide), 1600*w*, 1490*s*, 1385*w*, 1365*s*, 1315–1250*s*, 1220*s*, 1185*m*, 1095*w*, 1065*m*, 1035*w*, 1020*w*, 857*w*. ^{1}H-NMR (100 MHz, $CDCl_3$): 1.09 (*t*, *J* = 7.2, CH_3CH_2OCO–N); 1.28 (*t*, *J* = 7, 2 CH_3CH_2OCO–C(2)); 3.95 (*s*, CH_2Cl); 4.11 (*q*, *J* = 7.2, CH_3CH_2OCO–N); 4.34 (*q*, *J* = 7, CH_3CH_2OCO–C(2)); 4.37 (*q*, *J* = 7, CH_3CH_2OCO–C(2)); 7.20–7.78 (*m*, 9 arom. H); 7.92 (br. *s*, NH). Anal. calc. for $C_{24}H_{27}ClN_4O_7$ (518.95): C 55.55, H 5.24, Cl 6.83, N 10.80; found: C 55.82, H 5.22, Cl 6.88, N 10.87.

*5-(Chloromethyl)-1-[2-(*N*-ethoxycarbonyl-*N*-phenylamino)phenyl]-1*H*-1,2,4-triazole-3-carboxylic Acid* (**15**). A soln. of 146.5 g (0.282 mol) of **14** in 1466 ml of MeOH was added within 5 min to 848 ml (0.848 mol) of well stirred 1N NaOH precooled to 0°. The temp. of the mixture reached 22° and an initially formed precipitate redissolved gradually. Stirring was continued for 90 min at r.t., and the pH of the soln. was adjusted to 2 by slow addition of 2N HCl (*ca.* 450 ml). Cooling and seeding caused crystallization. After stirring for 3 h at 0°, the product was filtered, washed with 5 × 150 ml of H_2O and dried at 80° over $CaCl_2$ *in vacuo* to give a first crop (103.3 g) of **15**, m.p. 158° (sint.), 168–170° (dec.). Concentration of the mother liquor afforded another 7.5 g of **15** showing the same m.p. and the same single spot on TLC as the first crop. Total yield: 110.8 g (98%). TLC: R_f 0.71 (MeOH/AcOH 95:5). pK^* = 5.14 (equiv. mol. weight: 401). UV: 224 (sh). IR (CH_2Cl_2): 3500–2400*w* (OH ass.), 1760–1700*s* (C=O, acid and carbamate), 1600*w*, 1500*s*, 1365*s*, 1330–1260*s*, 1225*s*, 1140*m*, 1070*m*, 1045*m*, 1030*m*. ^{1}H-NMR (60 MHz, $CDCl_3$): 1.19 (*t*, *J* = 7, CH_3CH_2O); 4.16 (*q*, *J* = 7, CH_3CH_2O); 4.48 (*s*, CH_2Cl); 7.02–7.38 (*m*, 5 arom. H); 7.45–7.70 (*m*, 4 arom. H); 9.17 (*s*, COOH). Anal. calc. for $C_{19}H_{17}ClN_4O_4$ (400.82): C 56.94, H 4.28, Cl 8.85, N 13.98; found: C 57.10, H 4.41, Cl 8.88, N 13.88.

4,5-Dihydro-5-phenyl[1,2,4]triazolo[1,5-a]quinoxaline-2-carboxylic Acid (**16a**). A suspension of 53.8 g (134 mmol) of **15** in 280 ml of conc. (48%) HBr soln. was stirred under N_2 at 105° (bath temp.) for 22 h. Initially, a clear soln. resulted, but after 2 h, a bright crystalline precipitate appeared. The mixture was cooled to 10° and 300 ml of H_2O were added cautiously. After stirring for 3 h at 0°, the product was filtered, washed with 8 × 100 ml of H_2O, and dried at 80° over P_2O_5 *in vacuo* to give 37.48 g (96%) of **16a**. M.p. 190° (sint.), 205–207° (dec.). TLC: R_f 0.4 (tailing spot, MeOH/AcOH 95:5). pK^* = 4.92 (equiv. mol. weight: 294). UV: 233 (20800), 286 (8500), 336 (6080). IR (nujol): 3300–2380*m* (OH ass.), 1740*s* (C=O, acid), 1635*w*, 1605*m*, 1515*s*, 1490*s*, 1375*s*, 1315*m*, 1270*m*, 1235*w*, 1195*s*, 1170*s*, 1115*w*, 1085*w*, 1025*w*, 930*w*, 800*m*, 785*m*, 758*s*, 704*s*. ^{1}H-NMR (60 MHz, (D_6)DMSO): 5.11 (*s*, $CH_2(4)$); 6.70–7.50 (*m*, 8 arom. H); 7.73 (*dd*, *J* = 1.5, 8, H–C(9)); 9.95 (very br. *s*, COOH). Anal. calc. for $C_{16}H_{12}N_4O_2$ (292.30): C 65.75, H 4.14, N 19.17; found: C 65.54, H 4.13, N 19.15.

4,5-Dihydro-5-phenyl[1,2,4]triazolo[1,5-a]quinoxaline (**16b**). For 4 h, 3.8 g (13 mmol) of **16a** was decarboxylated in 80 ml of 2,2'-oxydiethanol under N_2 with 40 mg of Cu_2O at 135°. Workup according to the general procedure (decarboxylation of **8a**) afforded 2.9 g of crude **16b**. CC on 150 g of silica gel with toluene/AcOEt 9:1

followed by crystallization from CH_2Cl_2/hexane gave 1.71 g (53%) of **16b**. M.p. 102–105°. TLC: R_f 0.4 (toluene/AcOEt 6:4). UV: 229 (24920), 250 (sh), 288 (8440). IR (CH_2Cl_2): 3030*w*, 1625*w*, 1602*s*, 1540*m*, 1512*s*, 1502*s*, 1495*s*, 1460*m*, 1415*m*, 1380*s*, 1312*m*, 1300–1260*m*, 1240*w*, 1220*w*, 1175*s*, 1148*m*. ^{1}H-NMR (60 MHz, $CDCl_3$): 5.02 (*s*, CH_2(4)); 6.70–7.60 (*m*, 8 arom. H); 7.79 (*m*, H–C(9)); 8.02 (*s*, H–C(2)). Anal. calc. for $C_{15}H_{12}N_4$ (248.29): C 72.56, H 4.87, N 22.57; found: C 72.45, H 5.00, N 22.51.

Methyl 4,5-Dihydro-5-phenyl[1,2,4]triazolo[1,5-a]quinoxaline-2-carboxylate (**16c**). According to the general procedure (esterification of **8a**), 74.9 g (0.256 mol) of **16a** were esterified under N_2 in 1500 ml of MeOH with 300 ml of *ca.* 6M HCl/MeOH. The clear soln. was cooled and stirred in an ice/H_2O bath for 4 h. The crystalline product was filtered, washed with 250 ml of MeOH and dried over $CaCl_2$ *in vacuo* to give 69.4 g of crude **16c**. Recrystallization from CH_2Cl_2/i-PrOH afforded 65.6 g (84%) of **16c**. M.p. 147–149°. TLC: R_f 0.49 (toluene/AcOEt 6:4). UV: 234 (19500), 281 (8900), 341 (6100). IR (CH_2Cl_2): 1755*s* (C=O, ester), 1620*m*, 1520*s*, 1485*s*, 1455*m*, 1380*m*, 1325*m*, 1220*s* (O–C, ester), 1190*m*, 1175*m*, 1120*w*, 1025*w*, 833*w*. ^{1}H-NMR (100 MHz, $CDCl_3$): 4.06 (*s*, CH_3O); 5.07 (*s*, CH_2(4)); 6.78–7.50 (*m*, 8 arom. H); 7.93 (*dd*, J = 1.6, 8, H–C(9)). Anal. calc. for $C_{17}H_{14}N_4O_2$ (306.33): C 66.66, H 4.61, N 18.29; found: C 66.32, H 4.74, N 18.10.

4,5-Dihydro-5-phenyl[1,2,4]triazolo[1,5-a]quinoxaline-2-methanol (**16d**). A suspension of 64.4 g (0.21 mol) of **16c** in 644 ml of MeOH and 644 ml of THF was treated under N_2 with 30.2 g (0.789 mol) of $NaBH_4$ (added in 3 portions). The temp. of the mixture reached 30° and was controlled by cooling with ice/H_2O. Stirring was continued at 25° for 2 h. Then, 1300 ml of cold H_2O were added within 30 min. After stirring at 0° for 3 h, the crystals were collected, washed copiously with H_2O (final pH of the washings *ca.* 6), and dried over $CaCl_2$ *in vacuo* to give 54.3 g of crude **16d**. This was dissolved in 850 ml of MeOH and 130 ml of CH_2Cl_2 by gentle warming. The soln. was evaporated *in vacuo* (bath temp. 50°) until the final volume was *ca.* 500 ml. After standing overnight at 0°, the product was filtered, washed with MeOH, and dried at 80°/0.05 Torr for 16 h to give 49.5 g (85%) of **16d**. M.p. 184–188°. TLC: R_f 0.4 (CH_2Cl_2/MeOH 95:5). UV: 231 (22470), 253 (11340), 290 (8460). IR (nujol): 3350–3150*m* (OH, OH ass.), 1640*w*, 1605*w*, 1545*s*, 1500*s*, 1365*m*, 1355*m*, 1310*m*, 1280*s*, 1230*m*, 1215*m*, 1090*m*, 1055*s*, 1020*m*, 824*w*, 782*m*, 750*s*, 703*s*. ^{1}H-NMR (100 MHz, (D_6)DMSO): 4.58 (*d*, J = 6, becomes *s* after exchange with D_2O, CH_2OH); 5.07 (*s*, CH_2(4)); 5.41 (*t*, J = 6, exchangeable with D_2O, OH); 6.72–7.60 (*m*, 8 arom. H); 7.71 (*dd*, J = 2, 8, H–C(9)). Anal. calc. for $C_{16}H_{14}N_4O$ (278.32): C 69.05, H 5.07, N 20.13; found: C 68.9, H 5.2, N 20.1.

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