Nonsteroidal Antiinflammatory Agents, XVIII[1]:

C-5 Functionalized 6,7-Diphenyl-2,3-dihydro-1*H*-pyrrolizines as Inhibitors of Bovine Cyclooxygenase and 5-Lipoxygenase

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6-(4-Chlorophenyl)-7-phenyl-2,3-dihydro-1*H*-pyrrolizines with functional groups at position 5 of the heterocyclic moiety were synthesized and tested. To determine their antiinflammatory activity bovine blood was used as enzyme source for the cyclooxygenase and 5-lipoxygenase, respectively. The iminoxy acetic acid derivative and the iminotetrazole selectively inhibit the 5-lipoxygenase, all the other compounds show medium or low affinity to the active sites of cyclooxygenase and 5-lipoxygenase. In general all compounds inhibit 5-lipoxygenase more effectively than cyclooxygenase. Concerning the inhibition of 5-lipoxygenase the most active compounds found are equipotent to the corresponding propionic acid compounds, but they aren't well balanced dual inhibitors as shown for the carboxylic derivatives. A structure activity relationship and the enzyme selectivity are discussed.

Nichtsteroidale Antiphlogistika, 18. Mitt.[1]:
C-5-funktionalisierte 6,7-Diaryl-2,3-Dihydro-1*H*-Pyrrolizine als Inhibitoren der Rindercyclooxygenase und 5-Lipoxygenase

Die entzündungshemmende Aktivität von an C-5 funktionalisierten 6-(4-Chlorphenyl)-7-phenyl-dihydro-1*H*-pyrrolizinen wird beschrieben. Die aus Rinderblut gewonnenen Enzyme Cyclooxygenase und 5-Lipoxygenase werden für die Testung herangezogen. Das Iminoxyessigsäurederivat sowie das iminotetrazolsubstituierte Dihydropyrrolizin sind equipotent mit der korrespondierenden Propionsäure bezüglich der Inhibierung der 5-Lipoxygenase, sie besitzen jedoch nicht die ausgewogene duale Hemmwirkung der Carbonsäure. Die Hemmung beider Enzyme und die Enzymselektivität wird in Verbindung mit strukturellen Parametern diskutiert.

Many aromatic and heteroaromatic compounds with a carboxylic acid moiety are introduced in the therapy of rheumatoid diseases but many questions, *e.g.* inhibitory potency and structure, enzyme selectivity, mechanisms of action, are still unsatisfactory. Our experimental and pharmacological studies previously reported have indicated a high antiinflammatory activity of diaryldihydropyrrolizinyl carboxylic acids with an optimum for the 6-chlorophenyl and 7-phenyl-substituted compounds[2].

Based on these results it seemed reasonable to preserve this substitution pattern and to exchange the acidic moiety at C-5 of the heterocyclic nucleus. We here report the *in vitro* cyclooxygenase and 5-lipoxygenase inhibition of various 6,7-diaryl-2,3-dihydro-1*H*-pyrrolizines with different groups at C-5.

Chemistry

To modify the substitution pattern at C-5 we used the corresponding carbaldehyd **10** and the pyrrolizinyl oxalic acid chloride **2** as templates which were synthesized in good yield as reported[3)4)]. The oxime **11** and the oxime ether **12** are prepared according to *Unterhalt*[5)] and both compounds were characterized by their spectroscopic data (Table 1 and Exp. Part).

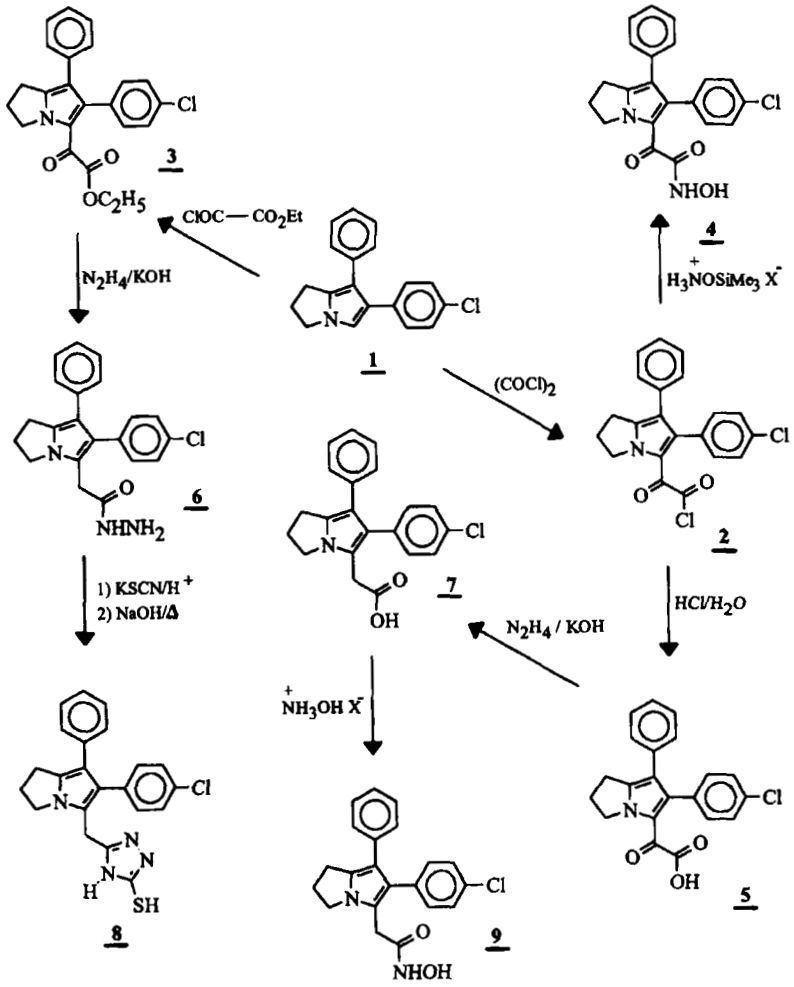
Especially for the oxime **11**, the oxime ether **12** and the iminoxycarboxylic acid derivative **13** spectroscopical

Table 1. Inhibition of bovine cyclooxygenase and 5-lipoxygenase by C-5 modified 6-(4-chlorophenyl)-7-phenyl-2,3-dihydro-1*H*-pyrrolizine derivatives

	% inhibition, conc. 10μM (IC 50)	
compound	CO	5-LO
4	0	20
5	10	35
6	12	43
7	85 (1,8)	100 (1,0)
8	71 (7)	39
9	8	44
11	0	33
12	0	0
13	5	100 (2,3)
14	56 (10)	100 (0,8)
15	9	18
Indomethacin	100 (0,0017)	--
NDGA	--	100 (0,52)

[+] Dedicated to Prof. Dr. *B. Unterhalt*, Münster, on the occasion of his 60th birthday.

  0365-6233/94/0808-0509 $ 5.00 + .25/0



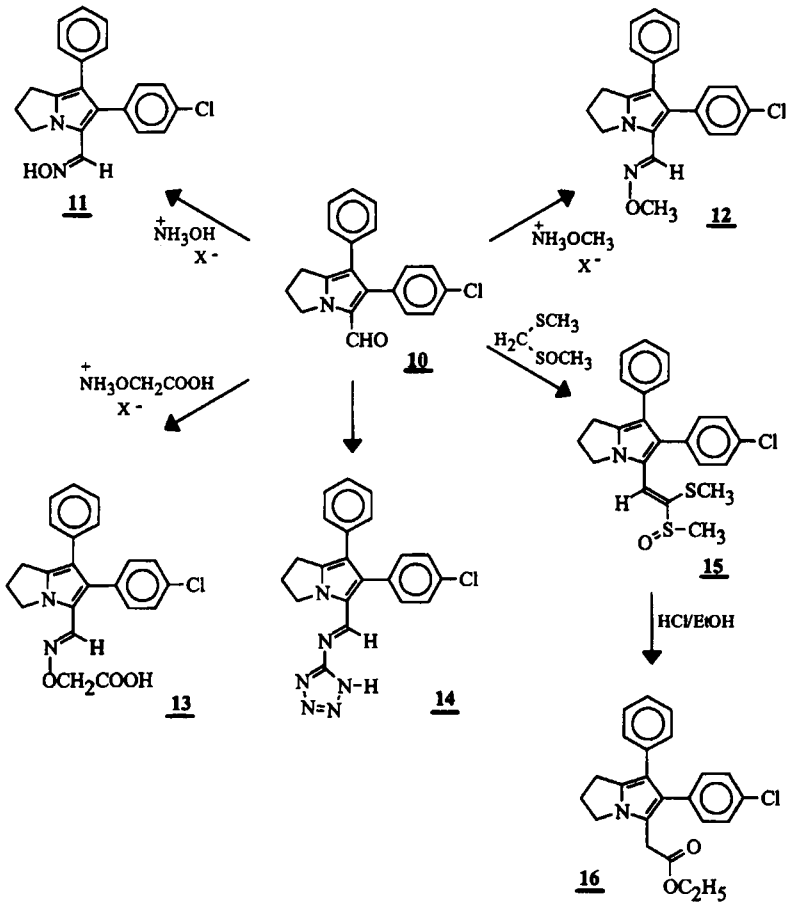
Scheme 1

experiments were made to elucidate the configuration. Investigations of the NOE-effects of the oxime **11** and the oxime ether **12** show that the vinyl-H is directly neighboured to the aromatic system indicating *E*-configuration.

Furthermore the configuration at the C=N-bond can be determined by the coupling constants of ^{13}CH-bonds. The magnitude of $^{1}J(^{13}CH)$ depends on the orientation of the lone electron pair of nitrogen to the CH-bond of the oxime. It is observed that "*trans*"-oximes are characterized by a $^{1}J(^{13}CH)$ = 163 Hz, "*cis*"-oximes by a $^{1}J(^{13}CH)$ = 177 Hz[6]. We found $^{1}J(^{13}CH)$ = 164 Hz for the oxime ether **12** resp. 165 for the iminoxy acetic acid **13** so that *E*-configuration of **12** and **13** is plausible.

On the one hand bioisosterism of the methylen iminoxymethyl moiety and the phenyl residue is discussed studying β-adrenergic systems[7], on the other hand potent inhibitors of the leukotriene biosynthesis are prepared using this group as pharmacophore[8] making this unit part of out interest. Reacting *O*-carboxymethyl hydroxylamine HCl and pyrrolizine carbaldehyd **10** in ethanol with $BaCO_3$ as a base the iminooxy derivative **13** was formed in good yield and was isolated without further purification. Its structure was verified by analytical and spectral data, *e.g.* two singletts at 4.6 and 8.0 ppm, respectively, indicating the methylen protons and the imino proton. MS cleavage of the N-O-bond in the EI mode led to formation of the corresponding nitrilium cations as base peak for all compounds with an iminooxy group (**11**, **12**, **13**).

It is known that the acidity of anthranilic acid derivatives is lower than that of the corresponding tetrazole systems[9]. Exchanging the carboxylic function by the tetrazole ring the higher metabolic stability of the tetrazoles may additionally increase the duration of effects. Thus, by refluxing 5-aminotetrazole, triethylamine, and the pyrrolizinyl carbaldehyde **10** the iminotetrazole derivative **14** was obtained in medium yield. The compound is characterized by the exchangeable signal of the NH-group at 13.5 ppm and loss of the tetrazole moiety in the MS leading to the corresponding iminium ion which loses 28 mass units forming the pyrrolizinyl carbenium-iminium ion. Condensation of methyl methylthiomethyl sulfoxide and the carbaldehyde **10** gave rise to a ketenedithioacetale **15**. In agreement with *Fraser* and *Wigfield's* investigations on monooxides of benzaldehyde ketenedithioacetals[10] the vinylic proton is diamagnetically shifted after addition of $Eu(fod)_3$ indicating *E*-configuration. After acidifying an ethanolic solution of the ketenedithioacetal with gaseous HCl the corresponding ethyl pyr-



Scheme 2

rolizinyl acetate **16** is formed. The spectroscopic data are in agreement with those of analogous derivatives[2]. For the synthesis of all other compounds see schemes 1, 2, and Exp. Part.

Table 2: Preparative and analytical data

compound	formula m_r	^{1}H-NMR (90 MHz, $CDCl_3$ δ (ppm))
3	$C_{23}H_{20}ClNO_3$ 393.5	1.03-1.08(t,3H,CH_3) 2.56-2.61(m,2H,C-2) 2.99-3.04(t,2H,C-1) 3.57-3.64(m,2H,-0-CH_2-) 4.45-4.50(m,2H,C-3) 6.97-7.27(m,9H,Arom.)
4	$C_{21}H_{17}ClN_2O_3$ 380.5	(d_6 DMSO) 2.50-2.53(m,2H,C2) 2.97-3.02(t,2H,J=7Hz,C-1) 4.27-4.35(t,2H,J=7Hz,C-3) 6.98-7.29(m,9H,Arom.) 8.87,11.01(s,1H,OH resp.NH, exchang.)
5	$C_{21}H_{16}ClNO_3$ 365.5	2.50-2.54(m,2H,C-2) 2.97-3.02(t,2H,J=7Hz,C-1) 4.32-4.37(t,2H,J=7Hz,C-3) 7.00-7.35(m,9H,Arom.) 13.6(s,broad,1H,COOH, exchang.)
6	$C_{21}H_{20}ClN_3O$ 365.6	2.53-2.60(m,2H,C-2) 3.01-3.06(m,2H,C-1) 3.60(s,2H,-CH_2-CO) 3.83(s,broad,2H,-NH_2) 3.94-3.98(m,2H,C-3) 6.75(s,broad,1H,-CO-NH-) 7.03-7.27(m,9H,Arom.)
7	$C_{21}H_{18}ClNO_2$ 351.4	2.51-2.61(m,2H,C-2) 3.01-3.06(t,2H,J=7Hz,C-1) 3.61(s,2H,-CH_2-COOH) 4.00-4.05(t,2H,J=7Hz,C=3) 7.05-7.27(m,9H,Arom.)
8	$C_{22}H_{19}ClN_4S$ 406.5	(d_6 DMSO) 2.44-2.50(m,2H,C-2) 2.91-2.93(m,2H,C-1)

Table 2: Continued.

		3.82-3.89(m,4H,C-3 and -CH_2-triazol) 6.98-7.34(m,9H,Aromat) 13.24(s,1H,exchang.) 13.31(s,1H,exchang.)
9	$C_{21}H_{10}ClN_2O_2$ 366.5	(d_6 DMSO) 2.43-2.50(m,2H,C-2) 2.91-2.96(t,2H,J=7Hz,C-1) 3.23(s,2H,-CH_2-CO-) 3.95(t,2H,J=7Hz,C-3) 6.97-7.29(m,9H,Arom.) 8.84(s,1H,exchang.) 10.56(s,1H,exchang.)
11	$C_{20}H_{17}ClN_2O$ 336.5	(d_6 DMSO) 2.47-2.54(m,2H,C-2) 2.95(t,2H,J=7Hz,C-1) 4.18(t,2H,J=7Hz,C-3) 7.01-7.40(m,9H,Arom.) 7.71(s,1H,H-C=N-O-) 10.86(s,1H,-N-OH,exchang.)
12	$C_{21}H_{19}ClN_2O$ 350.5	2.50-2.60(m,2H,C-2) 3.03(t,2H,J=7Hz,C-1) 3.87(s,3H,-CH_3) 4.29(t,2H,J=7Hz,C-3) 7.04-7,26(m,9H,Arom.) 7.85(s,1H,-H-C=N-O)
13	$C_{22}H_{18}ClN_2O_3$ 393.5	2.53-2.60(m,2H,C-2) 3.02 (t,2H,J=7Hz,C-1) 4.23(t,2H,J=7Hz,C-3) 4.65(s,2H,=N-O-CH_2-) 7.03-7.28(m,9H,Arom.) 7.98(s,1H,-CH=N-O-)
14	$C_{21}H_{17}ClN_6$ 388.6	(d_6 - (Aceton) 2.66-2.76(m,2H,C-2) 3.15(t,2H,J=7Hz,C-1) 4.58(t,2H,J=7Hz,C-3) 7.16-7.48(m,9H,Arom.) 8.83(s,1H,H-C=N-)
15	$C_{23}H_{22}ClNOS_2$ 427.5	2.13(s,3H,-S-CH_3) 2.54-2.59(m,2H,C-2) 2.67(s,3H,-SO-CH_3) 3.01-3,10(m,2H,C-1) 4.13-4.24(m,2H,C-3) 7.01-7.26(m,9H,Arom.) 7.46(s,1H=CH)

Results and Discussion

Inhibition of cyclooxygenase was determined by monitoring the formation of 12-hydroxyheptadecatrienoic acid (12-HHT) in bovine platelets; leukotriene B4 (LTB4) formed in bovine polymorphonuclear leucocytes (PMNLs) was used as an indicator of 5-lipoxygenase activity. For details concerning the testsystem, *e.g.* cell preparations, incubation procedures, sample preparations, reverse-phase HPLC, analysis statistics, and validity of results, see experimental protocols and reference[11]. Indomethacin, nordihydroguaretic acid (NDGA), and the corresponding pyrrolizinyl propionic acid derivative were applied as reference compounds.

All pyrrolizinyl derivatives functionalized at position 5 were investigated for their ability to inhibit bovine cyclooxygenase and 5-lipoxygenase. As documented in table 1 two of the compounds tested inhibit significantly the 5-lipoxygenase at the given doses. In particular, the highest inhibition was exhibited by the iminotetrazole derivative **14** which prevented the formation of LTB4 by 100% and of 12-HHT by 56% at 10 μM, the approximate IC 50 values were 0.8 μM and 10 μM, respectively. In the same experimental conditions the reference NDGA and indomethacin inhibit LTB4 and 12-HHT production by 100% each at a concentration of 3.3 μM. The iminoxy acetic acid derivative **13** shows higher 5-LO selectivity but a decreased inhibition of the cyclooxygenase. In general, oxime **11**, oxime ether **12**, α-ketoacid **5**, hydroxamic acid derivative **9** and the hydrazide **6** of the active pyrrolizinyl acetic acid **7** show lower inhibitory potencies or were completely inactive. All compounds are more efficient 5-lipoxygenase than cyclooxygenase inhibitors. The highest degree of selectivity was found in the iminoxy derivative **13**, the highest activity in the iminotetrazole compound **14**. However, both were less potent than the corresponding dihydropyrrolizinylic acids and the references NDGA and indomethacin. Remarkably reduced activity is observed testing the hydroxylamine **9** and hydrazide **6** of the acetic acid **7**: the inhibition of the cyclooxygenase is lowered to 8% and 12%, resp., keeping the 5-lipoxygenase inhibition in a medium range of 44% and 43%. None of the compounds tested is a potent and well balanced dual inhibitor of both 5-lipoxygenase and cyclooxygenase.

The significant inhibitory potency of both the iminoxy acetic acid **13** and the iminotetrazole **14** can be discussed using the 5-LO model of *Summers*[12]. In this model a planar W-conformation of the pentadien system is postulated as the bioactive form of endogenous arachidonic acid. Modelling studies show that both the iminoxycarboxylic acid **13** and the iminotetrazole **14** are complementary to the presumed W-conformation of arachidonic acid thus acting as inhibitors of the 5-lipoxygenase.

Hydrophobic interactions are as important as an acidic moiety at C-5. As previously shown by our experiments *E*-configuration of acrylic acid compounds is important for LO-inhibition[13]. The exocyclic double bond is directing the acidic moiety to the carboxylic binding site of the enzyme. Hydrogenation of the double bond leads to propionic acid derivatives with decreased inhibitory potency.

Both the iminoxy acetic acid **13** and the iminotetrazole **14** are characterized by an acidic function and an exocyclic double bond directing the acidic group towards the carbox-

ylic binding site. The exocyclic double bond seems to overlap complementary to the C-11/C-14-region of arachidonic acid and it can be postulated as a further binding site at the enzyme. Moreover, estimating relatively the length of the acidic side chains and the distance of the acidic function to the heterocycle, acrylic acid compounds and the iminotetrazole derivative are comparable documented by high inhibitory potency of both compounds.

Compounds lacking one or both of the structural requirements mentioned above are less potent or inactive. Thus, substances like the oxime ether **12** or the ketenedithioacetale **15** without acidic function but possessing an exocyclic double bond are inactive.

Additionally to CO-inhibition the pyrrolizinyl acetic acid derivative **7** is a potent inhibitor of the 5-LO. Introduction of a carbonyl function leads to the corresponding α-keto-acid **5** which is completely inactive. Obviously the polar keto function is not able to interact any longer with hydrophobic binding sites complementary to C-11/C-14 of arachidonic acid. Compared to the acetic acid derivative **7** the corresponding hydrazide **6** missing the acidic function shows low activity.

Further investigations including molecular modelling approaches are still under work.

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Experimental Part

Chemistry

Melting points: Büchi 510 apparatus, uncorrected.- IR-Spectra: Beckman acculab 3, KBr disks (unless otherwise stated).- ^{1}H-NMR Spectra: Brücker AC 300 (300 MHz), $CDCl_3$ (unless otherwise stated), using TMS as internal standard.- Analyses indicated by the elemental symbols were within ± 0.4% of the theoretical values.- All reagents were of analytical grade and obtained as follows: salts for buffer solutions, solvents: Merck, Darmstadt (Germany); calcium ionophore A 23187, NDGA, indomethacin: Sigma, München (Germany). HPLC reference substances LTB_4, 12-HHT, HPLC internal standards PGB_2 and 15-keto-PGE_2: Paesel, Frankfurt/Main (Germany). Bovine blood was obtained from the local slaughterhouse.

6-(4-Chlorophenyl)-7-phenyl-2,3-dihydro-1H-pyrrolizin (**1**)[14]

[6-(4-Chlorophenyl)-7-phenyl-2,3-dihydro-1H-pyrrolizin-5-yl)-glyoxylic acid chloride (**2**)

Oxalylchloride (2 mmol, 0.254 g) in absol. benzene (2 ml) is added dropwise to an ice-cooled solution of 2 mmol of **1**, dissolved in absol. benzene. After stirring for 3 h and another h at 50°C the solvent is evaporated. The residue is used without any further purification.

*[6-(4-Chlorophenyl)-7-phenyl-2,3-dihydro-1H-pyrrolizin-5-yl)-α-*oxocarboxylic-ethylester (**3**)

Ethyl oxalyl chloride (2 mmol) dissolved in 2 ml absol. benzene is added dropwise to an ice-cooled solution of **1**, dissolved in 5 ml absol. benzene. After stirring for 3 h and another h at 50°C the solvent is evaporated. After adding ether the product is obtained in yellow crystals.

*2-[6-(4-Chlorophenyl)-7-phenyl-2,3-dihydro-1H-pyrrolizin-5-yl)]-α-*glyoxolo-hydroxamic acid (**4**)

A solution of *O*-trimethylsilyl-hydroxylamine (11.7 mmol; 1.23 g) in 5 ml absol. CH_2Cl_2 is stirred at 0°C. A solution of **2** (2 mmol dissolved in 10 ml CH_2Cl_2) is added slowly. After removing the ice-bath the solution is stirred for 30 min at ambient temp. and another 12 h at 50°C. The solvent is evaporated, 6 ml 6N HCl are added to the residue and stirring is continued for 30 min. The product is extracted with ethyl acetate and the org. layer is dried over Na_2SO_4. After evaporating the solvent ether is added slowly and **4** begins to separate. For further purification the product is washed with ether.

*2-[6-[4-Chlorophenyl)-7-phenyl-2,3-dihydro-1H-pyrrolizin-5-yl)]-α-*oxo-carboxylic acid (**5**)

The acid chloride **2** is hydrolized with THF/water (1/1). Stirring is continued overnight. The solution is basified with 5% KOH (50 ml) and washed with ether several times. The alkaline solution is acidified with 2N HCl and extracted with ethyl acetate. After drying over Na_2SO_4 the solvent is evaporated. The residue is washed with ether.

[6-(4-Chlorophenyl)-7-phenyl-2,3-dihydro-1H-pyrrolizin-5-yl)-acetic acid hydrazide (**6**)

A mixture of **3** (2 mmol) and 12 ml hydrazine hydrate is stirred for 2 h at 130°C until the mixture has become nearly clear. The temp. is allowed to get to 100°C and solid KOH (15 g) is added. Stirring is continued for another h at this temp., the excess of hydrazine hydrate is removed by destillation after that time. The residue is diluted with water (100 ml) and the resulting aqueous layer is extracted with ethyl acetate. After evaporation of the solvent **6** is obtained as yellow substance. For further purification the product is washed with ether.

[6-(4-Chlorophenyl)-7-phenyl-2,3-dihydro-1H-pyrrolizin-5-yl]-acetic acid (**7**)

In this case **5** *is used as starting material.* **7** *is prepared according to* **6**. Working up is different from **6**: After dilution and extraction with ethyl acetate the alkaline solution is acidified with 6N HCl. The resulting acidic solution is extracted with ether, dried for some min, and the solvent is evaporated *in vacuo* at ambient temp. as fast as possible. The crude product is washed with cold ether and dried *in vacuo*.

3-[6-(4-Chlorophenyl)-7-phenyl-2,3-dihydro-1H-pyrrolizin-5-yl-methyl]-4H-5-mercapto-1,2,4-triazole (**8**)

Compound **6** (10 mmol), potassium thiocyanate (20 mmol) and 10 ml conc. HCl, diluted with 50 ml water, are refluxed for 2 h. After cooling to room temp. 150 ml water are added to the mixture which is extracted with ethyl acetate. After evaporating the solvent the residue is stirred with 50 ml 2M NaOH at 80°C for 1 h. The warm solution is filtered. After cooling the pH of the filtrate is adjusted with 6N HCl to 5-6. The solution is extracted with ethyl acetate, the org. layer is dried over Na_2SO_4. The solvent is evaporated, the product **8** is obtained as a white-grey powder.

2-[6-(4-Chlorophenyl)-7-phenyl-2,3-dihydro-1H-pyrrolizin-5-yl]-aceto-hydroxamic acid (**9**)

Compound **7** (14.5 mmol) and DMF (14.5 mmol; 1.06 g) are dissolved in 100 ml CH_2Cl_2 and cooled to 0°C. Oxalylchloride (32.6 mmol; 4.4 g) is added slowly and the reaction mixture is stirred for 40 min at room temp. This solution is added to a solution of hydroxylamine-HCl (58 mmol; 3.75 g) and triethylamine (87 mmol; 8.8 g) in THF/water (50 ml/10 ml). Stirring is continued for 45 min. The mixture is poured into 10 ml 2N HCl and

extracted with CH_2Cl_2. The org. layer is dried over Na_2SO_4 and the solvent is evaporated. The residue is purified by CC with ether to remove side products, the product **9** is eluted with ethyl acetate. The ethyl acetate fractions are evaporated. By adding diisopropyl ether the product **9** precipitated in white crystals.

[6-(4-Chlorophenyl)-7-phenyl-2,3-dihydro-1H-pyrrolizin-5-yl]-carbaldehyd (**10**)

10 mmol $POCl_3$ (1.53 g) are added to DMF (30 mmol, 2.19 g) at 0°C. The mixture is stirred at this temp. for 30 min. A solution of **1** (10 mmol dissolved in 10 ml absol. benzene) is added dropwise. The mixture is stirred for 5 h at 60°C. After adding 10 ml water the solution was made alkaline with NaOH 10%, the aqueous layer is extracted with CH_2Cl_2. The solvent is evaporated and **10** is isolated by CC (SiO_2/Ether:Hexan 3:1).

[6-(4-Chlorophenyl)-7-phenyl-2,3-dihydro-1H-pyrrolizin-5-yl]-aldoxime (**11**)

A solution of hydroxylamine-HCl (7 mmol; 0.485 g) and sodium acetate (5.6 mmol; 0.460 g, dissolved in 3 ml water) is stirred at 60°C. After addition of 4.7 mmol **10** dissolved in 10 ml THF the mixture is refluxed for 2 h. By addition of methanol white crystals begin to separate after 2 days. For further purification they were washed with cold methanol.

[6-(4-Chlorophenyl)-7-phenyl-2,3-dihydro-1H-pyrrolizin-5-yl]-O-methyl-aldoxime (**12**)

3.1 mmol (0.259 g) *O*-methylhydroxylamine-HCl, 3.1 mmol compound **10** and 0.9 g $BaCO_3$ are refluxed in 20 ml ethanol for 12 h. Ethanol is evaporated, water is added to the residue, and the aqueous layer is extracted with ether. By addition of ethanol to the ethereal phase **12** precipitated in white crystals.

[6-(4-Chlorophenyl)-7-phenyl-2,3-dihydro-1H-pyrrolizin-5-yl]-iminoxyacetic acid (**13**)

3.1 mmol (0.339 g) *O*-(carboxymethyl)-hydroxylamine-HCl, 3.1 mmol **10** and 0.9 g $BaCO_3$ in 20 ml ethanol are refluxed until the starting material has disappeared (tlc). The mixture is filtered and the solvent is evaporated *in vacuo*. After adding ether and standing overnight at 0°C the product **13** begins to separate in crystals.

[6-(4-Chlorophenyl)-7-phenyl-2,3-dihydro-1H-pyrrolizin-5-yl]-aldiminotetrazol (**14**)

5-Aminotetrazole-monohydrate is dehydrated at 100°C over P_2O_5 *in vacuo*. 10 mmol (0.860 g) 5-aminotetrazole and triethylamine (10 mmol; 1.01 g) are dissolved in 10 ml absol. methanol and the mixture is warmed up to 50°C. The carbaldehyde **10** is added as a solid to the mixture. DMSO is added dropwise until the mixture becomes a clear solution, then it is refluxed for 60 h. After cooling, filtration, and evaporation of the solvent the residue is purified over a short silicagel column with ethyl acetate. The org. solvent is evaporated, after addition of methanol compound **14** is precipitating.

1-Methylsulphinyl-1-methylthio-2-[6-(4-chlorophenyl)-7-phenyl-2,3-dihydro-1H-pyrrolizin-5-yl]-ethylen (**15**)

A solution of **10** (6.2 mmol, 2.01 g), methyl methylthiomethylsulphoxide (9.3 mmol; 1.15 g) in 10 ml THF and 2 ml Triton B solution (40% in methanol) is refluxed for 5 h. Addition of methyl methylthiomethylsulphoxide and Triton B is repeated. After refluxing for another 6 h, the solvent is evaporated and the residue is purified by CC (SiO_2/ethyl acetate). Compound **15** is obtained by removing the eluent on the rotavapor and adding methanol.

[6-(4-Chlorophenyl)-7-phenyl-2,3-dihydro-1H-pyrrolizin-5-yl]-acetic acid-ethylester (**16**)

300 mg of compound **15** are dissolved in 20 ml ethanol. Dry gaseous HCl is bubbled through the ice cooled solution for 1 min while the colour of the mixture is changing from yellow to dark green. The mixture is allowed to stand at room temp. for 30 min, then the solution is neutralized with 5% NaOH and the aqueous layer is extracted with ethyl acetate. The org. layer is washed with sodium bicarbonate solution, the org. solvent is evaporated. The product **16** is obtained in low yield by CC (SiO_2/CH_2Cl_2).

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