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Investigations in the Thiazolidine Series

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Several spirothiazolidines and *N*-acyl derivatives of ethyl thiazolidine-4-carboxylate have been synthetised. IR and NMR spectra have been studied. Pharmacological studies show GABA agonist activity for one of the spirothiazolidines and weak antimicrobial activity for two of them. No activity was apparent in a leukemia screen test.

Untersuchungen in der Thiazolidin-Reihe

Einige Spirothiazolidine und Amide des Thiazolidin-4-carbonsäureethylesters wurden synthetisiert und ihre IR- und NMR-Spektren studiert. Die pharmakologischen Untersuchungen ergaben für eines der Spirothiazolidine eine GABA-agonistische und für zwei eine schwache antimikrobielle Aktivität. Bei einem Leukämie-Screen-Test wurde keine Wirkung gefunden.

Numerous publications have shown the pharmacological interest of thiazolidine-4-carboxylic acid and its by-products which can have particularly an anti-inflammatory activity[1], a protective activity against radiations[2,3], an anti-hypertensive activity[4] or an activity against acne and seborrhea[5]. Moreover some spirothiazolidines can be used as intermediates for the synthesis of spiropenicillins[6]. But this chemical structure is principally known to be the subject of controversial discussion about its activity against cancer: some authors demonstrated this activity against cancer or leucocytopoiesis[7,8], others invalidated this activity[9].

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It appeared interesting to us to synthetise several derivatives of thiazolidine-4-carboxylic acid. With this object we have especially studied two short series of spirothiazolidines[6] **3** and the amides of the ethylester of the thiazolidine-4-carboxylic acid **4**.

A. Chemistry

Synthesis of the Spirothiazolidines **3**

Condensing mole by mole a cyclanone **1** with the ethylester of L-cysteine **(2)**, the corresponding spirothiazolidine **3** is obtained.

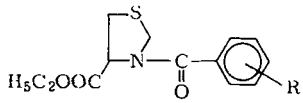
1 **2** **3**

This method of preparation is particularly simple and is only limited by the difficulty to separate the prepared compound from the original ester which have similar solubilities. This fact sometimes imposes a purification by sublimation (in hydrochloride form) and explains the relativly low yields in pure product.

Spectral Data: We obtained two kinds of N M R. spectra of each molecule, one as a hydrochloride and the other as a base. All the spirothiazolidines have the very same spectrum with the exception of the peaks deriving from the structure of the originating cyclanones. For example we give the spectrum of **3c**, in basic form: ^{1}H-N M R ($CDCl_3$): δ (ppm) = 1.2 (t; CH_3), 4.2 (q; CH_2), 2.95 and 3.4 (q; 2 H C-5), 3.9 (dd; J = 8.65/7.46 Hz, HC-4), 2.45 (wide band; NH), 1.6 and 2.3 (two hugebands; 8 H cyclopent.)

Synthesis of Amides of the Ethyl Ester of the Thiazolidine-4-carboxylic Acid **4**

These amides are synthetised by reaction of one mole of ethyl ester of the thiazolidine-4-carboxylic acid with half a mole of the corresponding acid chloride in solution in anhydrous benzene.



4

Spectral Data: For all the molecules of the serie we have obtained the very same spectra: ^{1}H-N M R ($CDCl_3$): δ (ppm) = 1.2 (t; CH_3), 4.2 (q; CH_2), 3.3 (q; 2 H C-5), 5.2 (q; H C-4), 4.6 (wide band; 2 H C-2), 8.3–7.2 (d and d; aromat.) moreover for **4a**: 2.3 (s; CH_3).

B. Pharmacological Data

None of the investigated compounds is very toxic: no mortality has been observed after giving a dose of 600 mg/kg per os or 400 mg/kg I. P. in mice. The amides of the thiazolidine-4-carboxylic ethyl-ester **4** given to a dose of 50 and 100 mg/kg per os in suspension in gum arabic in mice do not display any noticeable activity on the central nervous system in the following tests: traction, chimney, escaping, holed board, heated plate, electroshock.

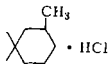
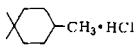
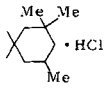
The spirothiazolidines have only a very weak antimicrobial activity against staphylococcus aureus and klebsellia pneumoniae. The tests executed according to the method of the dilution into liquid[10] gives C. M. I. near 40 to 60 mmole/ml. But, on the central nervous system, **3a** shows an interesting activity. Mice are dosed, i. p. followed 30 min and 5 h later by two separate injections of bicuculline (0.5 mg/kg). For **3a** inhibition of bicuculline convulsions was confirmed 30 min after injection of 300 mg/kg, i. p. suggesting possible direct GABA agonist effect, whereas there is no inhibition after the second injection, so there is no inhibition of GABA-transaminase enzyme. Compounds **3a, 3b** and **3d** have been tested for antileukemia activity; no effect has been detected.

We thank the Merieux Laboratories (Panlabs Inc.) and Boucharra Laboratories as also the National Cancer Institute in the U. S. A. that have been kind enough to take in charge the pharmacological tests.

Experimental Part

MP: Kofler apparatus; *I.R. spectra:* I.R. 4230 Beckman, KBr pellets; *N.M.R. spectra:* Hitachi Perkin Elmer R 24 (60 MHz in $CDCl_3$); *Analyses:* Service Central de Microanalyse du C.N.R.S., Lyon, France. Results of analyses agreed with calculated values. *Rotatory Power:* Polarimeter Perkin Elmer 241.

Table 1: *Spirothiazolidines*[c]

	R	Over all[a] Yield (%)	Crist. Solv.	I.R. (KBr)[d] cm^{-1}			$[\alpha]_{589}^{20}$[e]
				ν (NH)	ν (NC)	ν (CO_{ester})	
3a		41	ethanol/ether	3330	1300	1740	−80,4
3b		39	ethanol/ether	3340	1260	1740	−79,7
3c		20	Sublimation	3310	1230	1745	−80,6
3d		32	ethanol/ether or Sublimation	3320	1240	1745	−83,3

a) Yield of isolated pure product.
b) It is impossible to give exact melting points because these spirothiazolidines are sublimable.
c) The microanalyses were in satisfactory agreement with the calculated values : C: ±0.23; H: ±0.14; N: ±0.21. d) Measured with a spectrophotometer *Beckman 4230.* e) Measured with a polarimeter *Perkin-Elmer* 241.

Spirothiazolidines **3a–3d**

As an example we describe the preparation of **3c:** 0.03 mole of L-cysteine ethylester hydrochloride are refluxed for 15 min with 10 ml methanol and 0.1 mole of cyclopentanone. Stirring is carried on for 2 h at room-temp. The crude compound is obtained by precipitation with anhydrous ether. Purification is carried out by sublimation.

Amides **4a–4g**

0.1 mole of thiazolidine-4-carboxylic ethylester in 50 ml anhydrous benzene is kept for 4 h at room temp. with 0.05 mole of acid chloride. The hydrochloride produced is removed by filtration and the benzene evaporated. The residue is distilled (or recrystallized).

Table 2: *Amides*[b]

	R	Over all[a] Yield (%)	B.P.(°C) /mm Hg	M.P.(°C)	Crist. solv.	I.R. (KBr)[c] cm^{-1} $\nu(CH_{ali})$	$\nu(CH_{aro})$	$\nu(CO_{ester})$	$\nu(CO_{amide})$
4a	4-CH_3	86	201/0			2940	3010.1610.	1740	1640
4b	2-Cl	75	240/14			2950	3020.1610	1750	1650
4c	4-Cl	80	228/3			3000	3040.1610	1745	1650
4d	4-F	80	211/4			2950	3020.1610	1750	1650
4e	3-CF_3	72	144/34			2980	3020.1610	1750	1650
4f	4-NO_2	60		67	ethanol	3000	3080.1610	1745	1640
4g	3-NO_2 5-NO_2	65		84	ethanol	3000	3090.1610	1740	1645

a) Yield of isolated pure product. b) The microanalyses were in satisfactory agreement with the calculated value : C: ±0.23; H: ±0.15; S: ±0.20. c) Measured with a spectrophotometer *Beckman 4230.*

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Morphologische, Biochemische und Pharmakokinetische Untersuchungen an Saugblasen in Abhängigkeit von der Art und dem Zeitpunkt ihrer Entstehung

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In Untersuchungen an Ratten konnten keine Unterschiede im Elektrolyt- und Proteingehalt der Saugblasenflüssigkeit (SBF) von Blasen, die bei –160 bzw. –130 mm Hg entwickelt wurden, beobachtet werden. Bei einem Unterdruck von mehr als 180 mm Hg begann die Bildung von Hämatomen. In bereits bestehende Blasen strömen systemisch applizierte Pharmaka aufgrund von Diffusion ein, während bei sich bildenden Blasen zusätzlich eine Konvektion stattfindet. Werden die Blasen nicht während einer Verteilungsphase des Wirkstoffs entwickelt, so findet dennoch ein Konzentrationsausgleich zwischen der interstitiellen Flüssigkeit, welche die Blase umgibt, und der Blasenflüssigkeit statt. Die Pentrationsgeschwindigkeit in SBF bereits bestehender Blasen wird auch von der Blasengröße bestimmt.

Morphological, Biochemical and Pharmacokinetic Investigations of Suction Blisters. Influence of Mode and Time of Blister Development

Investigations in rats proved the concentrations of electrolytes and proteins in skin suction blister fluid (SBF) to be identical for blisters set up at –160 or –130 mm Hg. Haematomas ocurred at pressures below –180 mm Hg. Systemically administered drugs penetrate into SBF by diffusion, if the blisters are raised prior to drug administration. Into developing blisters drugs penetrate also by convection. Distribution equilibrium is established between SBF and surrounding tissue fluid, if blisters are not raised during a distribution phase. The penetration rate into the SBF of blisters raised prior to drug administration is determined in part by blister volume.

Seit den grundlegenden Untersuchungen von *Dost* hat sich die Pharmakokinetik zu einem Arbeitsgebiet entwickelt, das wichtige neue Erkenntnisse über Arzneimittel ermöglichte. Pharma-

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