λmax = 275, 233 nm. ^{1}H-NMR ($CDCl_3$): δ (ppm) = 7,18 (d, 1H, H-2); 6,80 (d, 1H, H-3); 6,15–5,50 (m, 1H, H-2'); 5,30–4,85 (m, 2H, H-3'); 3,50 (t, 1H, H-4); 3,27–2,25 (m, 4H, H-6, H-7); 2,88 (d, 2H, H-1'); 2,45 (s, 3H, NCH_3). IR (Film): 2800 (NCH_3), 1658 cm^{-1} (C=C, Alken).

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Arch. Pharm. (Weinheim) *316*, 141–146 (1983)

Potential Antitumor Agents, VIII[1)]

Allyl, Propargyl and Cyanomethyl Esters of Imidazo[2,1-*b*]thiazole-5-carboxylic Acids[+)]

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Eingegangen am 28. Januar 1982

The imidazo[2,1-*b*]thiazole-5-carboxylic acids **1** and **2** were used as starting materials for the synthesis of allyl **3a–c**, **6a–c**, propargyl **4a–c**, **7a–c** and cyanomethyl esters **5a–c**, **8a–c**. Under the conditions employed these compounds did not show significant antitumor activity.

Potentielle Tumorhemmende Wirkstoffe, 8. Mitt.:[1)]
Allyl-, Propargyl- und Cyanomethyl-Ester von Imidazo[2,1-*b*]thiazol-5-carbonsäuren

Die Imidazo[2,1-*b*]thiazol-5-carbonsäuren **1** und **2** wurden als Ausgangsstoffe zur Synthese der Allyl- **3a–c**, **6a–c**, Propargyl- **4a–c**, **7a–c** und Cyanomethyl-Ester **5a–c**, **8a–c** verwendet. Unter den Versuchsbedingungen zeigten diese Verbindungen keine signifikanten tumorhemmenden Effekte.

[+)] Dedicated to Prof. *M. Amorosa* on the occasion of his 70th birthday.

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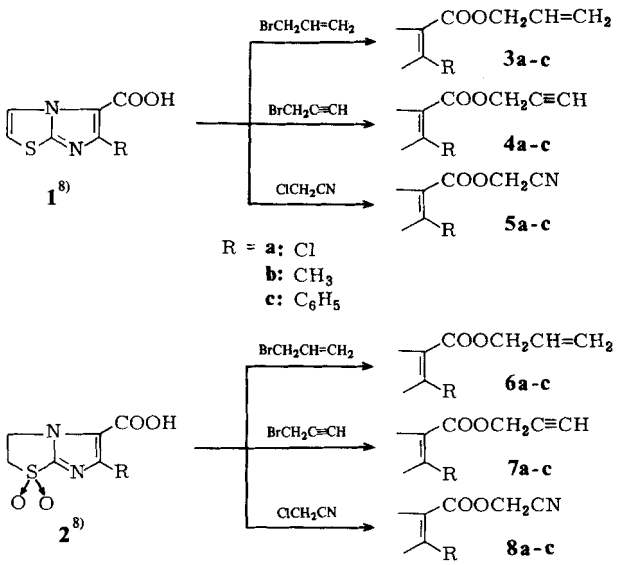
Bodor and *Kaminski* recently reported the synthesis of halogenated esters of carboxylic acids as soft alkylating compounds: one of these esters was found to have anticancer activity[2]. A few years ago *Loeffler* and coworkers described the antitumor activity of halogenated esters of several amino acids: a similar activity was found in other activated esters such as allyl, propargyl, cyanomethyl and vinyl esters[3-5]. A great number of pyrimidones were synthesized as potential antineoplastic agents[6]: one of these, a propargyl derivative, has received particular attention[7]. In this paper we wish to report the synthesis of allyl, propargyl and cyanomethyl esters of the imidazo[2,1-*b*]thiazole-5-carboxylic acids **1** and **2** (see Scheme 1).



1[8] 2[8]

Chemistry

We have already described the synthesis of compounds **1** and **2** by oxidation of the corresponding 5-formyl derivatives[8]; the reaction of the acids **1** and **2** with allyl bromide, propargyl bromide and chloroacetonitrile gave the corresponding esters **3a–c–5a–c** and **6a–c–8a–c** (see Table 1). These compounds were identified on the basis of their analytical and spectroscopic data.

The IR spectra of compounds **5a–c** and **8a–c** do not show the band of the cyano group for the presence of an electron attracting atom placed on the α-carbon of the cyano group[9-11]. The ^{1}H-NMR spectra of compounds **3a–c–5a–c** (see Table 2) show, in the aromatic region, two hydrogens at δ ca. 7.0 and 8.2 (J = 4.2 Hz), relative to H-2 and H-3, resp.: these values are in agreement with those previously reported[11]. The ^{1}H-NMR spectra of compounds **6a–c–8a–c** show two multiplets at δ ca. 4.2 and 4.8 relative to the two hydrogens of C-2 and C-3, resp. The chemical shifts of the multiplets relative to the C-3 hydrogens of compounds **6a–c** are not reported in Table 2 under column H-3, since they overlap the doublet of the allyl group. The chemical shifts of the C-2 and C-3 hydrogens for compounds **6a–c–8a–c** are in agreement with those previously described[8]. The chemical shifts of aliphatic hydrogens for compounds **3a–c–8a–c** are consistent with allyl, propargyl and cyanomethyl groups (see Table 2).

Table 1: *Allyl, Propargyl and Cyanomethyl Esters of Imidazo[2,1-b] thiazole-5-carboxylic acids*

Compd.	mp °C	IR cm^{-1}	Formula (m. W.)	Calcd. Found C	H	N
3a	93–94	3140–3090; 1685	$C_9H_7ClN_2O_2S$ (242.7)	44.5 44.4	2.91 2.99	11.5 11.7
3b	65–67	3150–3310; 1680	$C_{10}H_{10}N_2O_2S$ (222.3)	54.0 54.1	4.53 4.50	12.6 12.9
3c	57–59	3130; 1700	$C_{15}H_{12}N_2O_2S$ (284.3)	63.4 63.8	4.25 4.40	9.8 10.0
4a	123–124	3250–3170–3125; 2120; 1695	$C_9H_5ClN_2O_2S$ (240.7)	44.9 45.1	2.09 2.31	11.6 11.4
4b	131–134	3135; 2110; 1705	$C_{10}H_8N_2O_2S$ (220.2)	54.5 54.2	3.66 3.57	12.7 12.3
4c	116–118	3180–3150–3110; 2110; 1685	$C_{15}H_{10}N_2O_2S$ (282.3)	63.8 63.5	3.57 3.55	9.9 9.8
5a	161–163	3130; 1695	$C_8H_4ClN_3O_2S$ (241.6)	39.8 39.5	1.67 1.58	17.4 17.4
5b	125–127	3150–3125; 1710	$C_9H_7N_3O_2S$ (221.2)	48.7 48.4	3.20 3.41	19.0 18.8
5c	158–160	3090; 1675	$C_{14}H_9N_3O_2S$ (283.3)	59.3 59.5	3.20 3.12	14.8 14.8
6a	182–185	1710	$C_9H_9ClN_2O_4S$ (276.7)	39.1 39.3	3.28 3.20	10.1 9.7
6b	127–130	1700	$C_{10}H_{12}N_2O_4S$ (256.3)	46.9 46.8	4.72 4.82	10.9 10.6
6c	117–120	1720–1705	$C_{15}H_{14}N_2O_4S$ (318.3)	56.6 56.3	4.43 4.35	8.8 8.5
7a	160–161	3300; 2140; 1710	$C_9H_7ClN_2O_4S$ (274.7)	39.3 39.5	2.57 2.50	10.2 10.0
7b	136–138	3270; 2125; 1710	$C_{10}H_{10}N_2O_4S$ (254.3)	47.2 47.4	3.96 3.93	11.0 11.0
7c	185–187	3265; 2120; 1725	$C_{15}H_{12}N_2O_4S$ (316.3)	56.9 56.9	3.82 3.74	8.9 8.8
8a	176–177	1720	$C_8H_6ClN_3O_4S$ (275.7)	34.8 35.2	2.19 2.31	15.2 15.0
8b	133–136	1735	$C_9H_9N_3O_4S$ (255.2)	42.3 42.7	3.55 3.58	16.5 16.4
8c	215–217	1700	$C_{14}H_{11}N_3O_4S$ (317.3)	53.0 52.9	3.49 3.45	13.2 13.0

Table 2: *^{1}H-N.M.R. Spectra of the esters* **3a–c – 8a–c** (δ = ppm)

Compd.	CH_3	C_6H_5	H-2	H-3	$J_{2,3}$ (Hz)	-COOR′
3a	–	–	7.08(1H)	8.20(1H)	4.2	4.90(2H,d,-$CO_2\underline{CH_2}$–); 5.30 (2H,m,–CH=$\overline{CH_2}$); 6.03(1H, m,–CH_2–$\underline{CH}$=$\overline{CH_2}$).
3b	2.61	–	6.90(1H)	8.08(1H)	4.2	4.83(2H,d,–$CO_2\underline{CH_2}$–); 5.30 (2H,m,–CH=$\overline{CH_2}$); 6.03(1H, m,–CH_2–$\underline{CH}$=$\overline{CH_2}$).
3c	–	7.3–7.6(3H) 7.8–8.0(2H)	6.96(1H)	8.21(1H)	4.2	4.80(2H,d,–$CO_2\underline{CH_2}$–); 5.23 (2H,m,–CH=$\overline{CH_2}$); 5.96 (1H, m,–CH_2–$\underline{CH}$=CH_2).
4a	–	–	7.18(1H)	8.25(1H)	4.2	2.61(1H,t,≡CH,J=2.4Hz); 5.0 (2H,d,–$\underline{CH_2}$–C≡CH,J=2.4Hz).
4b	2.63	–	6.93(1H)	8.28(1H)	4.2	2.53(1H,t,≡CH,J=2.4Hz); 4.95 (2H,d,–$\underline{CH_2}$–C≡CH,J=2.4Hz).
4c	–	7.4–7.6(3H) 7.8–8.0(2H)	7.00(1H)	8.23(1H)	4.2	2.50(1H,t,≡CH,J=2.4Hz); 4.85 (2H,d,–$\underline{CH_2}$–C≡CH,J=2.4Hz).
5a	–	–	7.18(1H)	8.16(1H)	4.2	5.01(2H,s,–CH_2CN).
5b	2.65		7.00(1H)	8.10(1H)	4.2	5.00(2H,s,–CH_2CN).
5c	–	7.3–7.6(3H) 7.7–7.9(2H)	7.03(1H)	8.16(1H)	4.2	4.85(2H,s,–CH_2CN).
6a	–	–	4.22(2H)	–		4.80(4H,m,H_2–3 + –CH_2–CH=); 5.4(2H,m,–CH=$\overline{CH_2}$); 6.04 (1H, m,–CH_2–$\underline{CH}$=$\overline{CH_2}$).
6b	2.48	–	4.22(2H)	–		4.75(4H,m,H_2–3 + –CH_2–CH=); 5.36(2H,m,–CH=$\overline{CH_2}$); 6.06 (1H,m,–CH_2–$\underline{CH}$=$\overline{CH_2}$).
6c	–	7.4–7.6(3H) 7.7–7.8(2H)	4.30(2H)	–		4.82(4H,m,H_2–3 + –CH_2–CH=); 5.28(2H,m,–CH=CH_2); 5.96 (1H,m,–CH_2–$\underline{CH}$=$\overline{CH_2}$).
7a	–	–	4.23(2H)	4.80(2H)		3.68(1H,t,≡CH,J=2.4Hz); 5.02 (2H,d,–$\underline{CH_2}$–C≡CH,J=2.4Hz).
7b	2.52	–	4.22(2H)	4.74(2H)		3.66(1H,t,≡CH,J=2.4Hz); 5.02 (2H,d,–$\underline{CH_2}$–C≡CH,J=2.4Hz).
7c	–	7.4–7.5(3H) 7.7–7.8(2H)	4.26(2H)	4.82(2H)		3.62(1H,t,≡CH,J=2.4Hz); 4.92 (2H,d,–$\underline{CH_2}$–C≡CH,J=2.4Hz).
8a	–	–	4.26(2H)	4.80(2H)		5.30(2H,s,–CH_2CN).
8b	2.50	–	4.21(2H)	4.75(2H)		5.27(2H,s,–CH_2CN).
8c	–	7.4–7.5(3H) 7.7–7.8(2H)	4.30(2H)	4.80(2H)		5.20(2H,s,–CH_2CN).

Pharmacological Results

For the antitumor tests, female Swiss mice (average weight 21 ± 1 g) were implanted on day 0 with 10^6 Ehrlich ascites tumor cells from donor mice housed in these laboratories. The compounds tested were dissolved in DMSO. Each compound was injected at 100–20–4 mg/kg i.p. 24 h after tumor implantation except compounds **3a–5a** and **3b** which were injected at 50–10–2 mg/kg and compound **5c** which was injected at 20–4–0.8 mg/kg (four mice/group). The amount of DMSO (5 ml/kg), previously used in analogous experiments, did not affect tumor growth. Deaths were recorded for the period of 30 days. The activity was measured as the ratio of the mean survival time of the test animals to that of the control animals expressed as a percentage (% T/C). Significant activity is achieved with an increased life span of 25 % (T/C ≥ 125). The compounds tested did not show a significant antitumor activity under these experimental conditions.

Experimental

MP: uncorr. The extracts were dried on anhydrous Na_2SO_4 and the organic solvents were evaporated under reduced pressure. Bakerflex plates (silica gel IB2-F) were used for TLC; petroleum ether (bp 60–80°)/acetone mixtures were employed in various proportions as eluents. *IR spectra:* (Nujol) Perkin Elmer 298. *^{1}H-NMR spectra:* ($CDCl_3$: **3a–c–5a–c**) (d_6-DMSO: **6a–c–8a–c**) Varian XL-100, TMS int. stand.

General procedure for the allyl esters: **3a–c, 6a–c**

The acid (**1** or **2**, 5 mmol) was dissolved in the minimum amount of THF and treated with 10 mmol allyl bromide and 5 mmol triethylamine. The reaction mixture was refluxed for 2–6 h (according to a TLC test), the solvent was evaporated and the residue, dissolved in $CHCl_3$, was washed with 5 % $NaHCO_3$. The unreacted acid was recovered treating this alkaline solution with 2N-HCl, while the crude ester was obtained by evaporating the chloroform. The allyl esters were crystallized from ethanol (compound **3c** from petroleum ether) with a yield of about 90 % (calcd. on the amount of reacted acid).

General procedure for the propargyl: **4a–c. 7a–c** *and cyanomethyl esters* **5a–c, 8a–c**

With the same procedure above described, the acid (5 mmol) was treated with 15 mmol propargyl bromide or chloroacetonitrile and 5 mmol triethylamine. The esters were crystallized from ethanol with a yield of about 50 % for the propargyl esters and about 80 % for the cyanomethyl esters (calcd. on the amount of reacted acid).

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Cyclische Aldehydderivate als Alkylierungsreagenzien, 1. Mitt.

Acyclo- und Azaacycloanaloga von Nucleosiden

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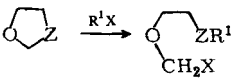
Ringöffnung von 1,3-Dioxolan und von 3-Alkyl-1,3-oxazolidinen mit Acetylchlorid oder Trimethyliodsilan führt zu den α-Halogenethern **2a–2e**. Diese stellen Alkylierungsreagenzien dar. Ihre Umsetzung mit Adenin, 6-Chlorpurin oder silyliertem Cytosin bzw. silylierten Uracilderivaten gibt die 2-Hydroxyethoxymethyl- bzw. 2-Acetamidoethoxymethylverbindungen **4**, **5** und **7**.

Cyclic Aldehyde Derivatives as Alkylating Reagents, I: Acyclo and Azaacyclo Analogs of Nucleosides

Ring opening of 1,3-dioxolane and of 3-alkyl-1,3-oxazolidines with acetyl chloride or trimethyliodosilane leads to the α-halogeno ethers **2a–2e**. These are alkylating reagents. Their reactions with adenine, 6-chloropurine, silylated cytosine or silylated uracil derivatives gives the 2-(hydroxy)ethoxymethyl- or 2-(acetamido)ethoxymethyl compounds **4**, **5** and **7**.

Cyclische Aldehydderivate wie 1,3-Dioxolane[1] oder 3-Alkyl-1,3-oxazolidine[2] geben unter Säurekatalyse mit reaktiven Olefinen wie Enolethern[1,2] oder Enaminen[3] in einer polaren Cycloaddition Perhydro-1,4-dioxepine und -1,4-diazepine. In einigen Fällen wurde daneben auch die Bildung acyclischer Reaktionsprodukte beobachtet[4]. Mechanistisch betrachtet verlaufen diese Umsetzungen über das ringgeöffnete Produkt **2**, das elektrophil mit dem Olefin reagiert[5].



1 **2**

1, 2	Z	R^1	X
a	O	Ac	Cl
b	O	$Si(CH_3)_3$	I
c	NCH_3	Ac	Cl
d	$NCH_2C_6H_5$	Ac	Cl
e	$NCH_2C_6H_5$	$CO_2CH_2C_6H_5$	Cl

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