DC Fließmittel A	Rf monoiodierte Form	Rf diiodierte Form
10	0.58	0.66
11	0.59	0.68
12	0.56	0.74

Literatur

1 M. Blau und H.F. Kung, Radiopharm. 2, Proc. Int. Symp., p. 671–683, Ed. J. Sorenson, Am. Soc. Nucl. Med., New York, N.Y. 1979.
2 K. Rehse, G. Schachschneider, H. Wenzel und N. Rietbrock, Arch. Pharm. (Weinheim) *312*, 322 (1979).
3 S.M. Chan, G.P. Basmadjiyn, D.F. Marten, S.A. Dadek, R.A. Magarian, J.R. Grunder und R.D. Jce, J. Lab. Comp. Radiopharm. *20*, 1017 (1983).
4 E. Röder, P.H. Focken, H.J. Biersack und C. Winkler, IRCS Med. Sci. Pharmakol. *5*, 542 (1977).
5 S. Smith, J. Chem. Soc. *1935*, 1305.
6 E. Röder und P.H. Focken, J. Lab. Comp. Radiopharm. *15*, 197 (1978).
7 W.M. Hunter und F.C. Greenwood, Nature (London) *194*, 495 (1962).

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Potential Antitumor Agents, XV[1)]

Anthraquinone Derivatives[+)]

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The synthesis of hydroxyalkylamino derivatives from 1,8-dichloroanthraquinone and succinic esters from hydroxyanthraquinones is reported. The esters **10** and **12** show significant antitumor activity but without improvement in comparison to the activity of a previously described analogue.

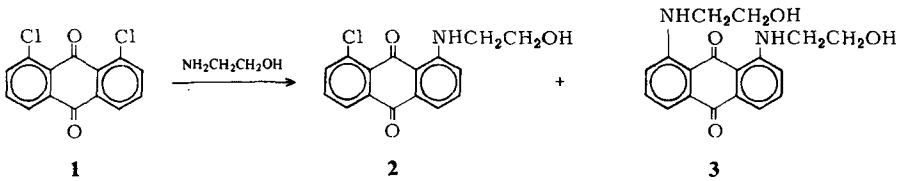
Potentielle Antitumor-Wirkstoffe, 15. Mitt.: Anthrachinon-Derivate

Es wird über die Synthese von Hydroxyalkylaminoderivaten des 1,8-Dichloranthrachinons und von Bernsteinsäureestern von Hydroxyanthrachinonen berichtet. Die Ester **10** und **12** zeigen eine signifikante Antitumorwirkung, jedoch keine Verbesserung im Vergleich mit der Wirkung eines früher beschriebenen Analogen.

In our previous paper on anthraquinone derivatives as potential antitumor agents[1] we reported a number of references on this topic; the continuing interest for this class of compounds is confirmed by the most recent papers[2-9]. Our previous paper reported the synthesis of two groups of compounds: esters from 1,8-dihydroxyanthraquinone and alkylamino derivatives from 1,8-dichloroanthraquinone (**1**). The antitumor activity shown by the succinic esters[1] led us to prepare new esters from different hydroxyanthraquinones. Furthermore, new hydroxyalkylamino derivatives were prepared from compound **1**.

Chemistry

The reaction of **1** with monoethanolamine in pyridine yielded two derivatives: compound **2**, as expected, was identical to that obtained by reacting **1** with diethanol-



1 **2** **3**

amine[1]. Compound **3** and the other derivatives **4–9** prepared from different hydroxyalkylamines are listed in Table 1. The esters **10–14** were prepared by treating the hydroxyanthraquinone, dissolved in pyridine, with ethyl succinyl chloride (Table 1). Table 2 shows the IR and ^{1}H-NMR data of all the new compounds **3–14**.

Table 1: *Analytical data and antitumor activity of the anthraquinones* **3–14**

Compd.	Substituents* in					Formula (mw)	Calcd. / Found			mp °C	Recryst. solvent	% T/C (dose mg/kg)	
	1	2	4	5	6 8		C	H	N			Single dose treatment	Repeated dose treatment
3	$NHCH_2CH_2OH$	–	–	–	– $NHCH_2CH_2OH$	$C_{18}H_{18}N_2O_4$	66.2	5.56	8.6	260–265	EtOH		
						(326.3)	65.9	5.47	8.3				
4	Cl	–	–	–	– $NH(CH_2)_3OH$	$C_{17}H_{14}ClNO_3$	64.7	4.47	4.4	152–155	Pt.Et.		
						(315.7)	65.2	4.43	4.3				
5	$NH(CH_2)_3OH$	–	–	–	– $NH(CH_2)_3OH$	$C_{20}H_{22}N_2O_4$	67.8	6.26	7.9	215–220	EtOH		
						(354.4)	67.5	6.09	8.2				
6	Cl	–	–	–	– $NH(CH_2)_4OH$	$C_{18}H_{16}ClNO_3$	65.5	4.89	4.2	145–148	EtOH		
						(329.8)	65.4	4.97	4.0				
7	$NH(CH_2)_4OH$	–	–	–	– $NH(CH_2)_4OH$	$C_{22}H_{26}N_2O_4$	69.1	6.85	7.3	203–206	EtOH		
						(382.4)	69.0	7.14	7.2				
8	Cl	–	–	–	– $NH(CH_2)_5OH$	$C_{19}H_{18}ClNO_3$	66.4	5.28	4.1	118–123	EtOH		
						(343.8)	66.3	5.48	3.9				
9	$NH(CH_2)_5OH$	–	–	–	– $NH(CH_2)_5OH$	$C_{24}H_{30}N_2O_4$	70.2	7.37	6.8	139–143	EtOH		
						(410.5)	70.0	7.21	7.0				
10	S	S	–	–	– –	$C_{26}H_{24}O_{10}$	62.9	4.87		83–85	EtOH	130	140
						(496.4)	63.0	4.86				(200)	(3 x 100)
11	S	–	S	–	– –	$C_{26}H_{24}O_{10}$	62.9	4.87		118–120	EtOH		
						(496.4)	62.7	4.74					

Forts. **Table 1:**

Compd.	Substituents* in					Formula (mw)	Calcd. / Found		mp °C	Recryst. solvent	% T/C (dose mg/kg)	
	1	2	4	5	6	8		C	H			Single dose treatment	Repeated dose treatment
12	–	S	–	–	S	–	$C_{26}H_{24}O_{10}$ (496.4)	62.9 62.7	4.87 4.76	148–151	EtOH	130 (40)	126 (3 x 100)
13	S	S	S	–	–	–	$C_{32}H_{32}O_{14}$ (640.6)	60.0 60.2	5.04 4.89	123–127	EtOH		
14	S	S	–	S	–	S	$C_{38}H_{40}O_{18}$ (784.7)	58.2 58.3	5.14 4.88	113–115	EtOH		

* S = $OCOCH_2CH_2COOC_2H_5$

Table 2: *IR and ^{1}H-NMR data of the anthraquinones* **3–14**

Compd.	ν_{max} (cm^{-1})	δ (ppm) in d_6-DMSO)
3	3370, 1620, 1300	3.45(4H,m,CH_2); 3.78(4H,m,CH_2); 5.07(2H,t,OH); 7.35–7.90(6H,m,arom.); 10.03(2H,t,NH)
4	3500–3100, 1630, 1310	1.88(2H, quint,CH_2); 3.45(2H,m,CH_2); 3.70(2H,m,CH_2); 4.81(1H,t,OH); 7.35–8.25(5H,m,arom.); 8.25–8.45(1H, m,arom.); 9.80(1H,t,NH)
5	3380, 1610, 1300	1.80(4H,quint,CH_2); 3.41(4H,m,CH_2); 3.68(4H,m,CH_2); 4.76(2H,t,OH); 7.25–7.40(2H,pseudo-q,arom.); 7.50–7.85(4H,m,arom.); 9.84(2H,t,NH)
6	3600–3200, 1635, 1310	1.74(4H,m,CH_2); 3.33(2H,m,CH_2); 3.60(2H,m,CH_2); 4.70(1H,t,OH); 7.23–8.20(5H,m,arom.); 8.20–8.43 (1H,pseudo-q,arom.); 9.75(1H,t,NH)
7	3400, 1620, 1205	1.74(8H,m,CH_2); 3.30(4H,m,CH_2); 3.65(4H,m,CH_2); 4.70(2H,t,OH); 7.15–7.35(2H,m,arom.); 7.50–7.85 (4H,m,arom.); 9.80(2H,t,NH)
8	3500–3100, 1640, 1310	1.60(6H, broad,CH_2); 3.30(2H,m,CH_2); 3.55(2H,m,CH_2); 4.58(1H,t,OH); 7.23–8.25(5H,m,arom.); 8.25–8.45(1H, m,arom.); 9.75(1H,t,NH)
9	3280, 1615, 1210	1.58(12H, broad,CH_2); 3.27(4H,m,CH_2); 3.60(4H,m, CH_2); 4.60(2H,t,OH); 7.15–7.38(2H,m,arom.); 7.50–7.87(4H,m,arom.); 9.80(2H,t,NH)
10	1775, 1730, 1675, 1585	1.20(6H,t,$CH_2\underline{CH_3}$); 2.82(4H,m,CH_2CH_2); 3.10(4H,m, CH_2CH_2); 4.28(4H,q,$\underline{CH_2}CH_3$); 8.08–8.32(3H,m,arom.); 8.32–8.62(3H,m,arom.)
11	1765, 1725, 1670, 1585	1.27(6H,t,$CH_2\underline{CH_3}$); 2.85(4H,m,CH_2CH_2); 3.10(4H,m, CH_2CH_2); 4.28(4H,q,$\underline{CH_2}CH_3$); 7.98(2H,s,arom.); 8.10–8.30(2H,m,arom.); 8.30–8.50(2H,m,arom.)
12	1750, 1735, 1665, 1590	1.20(6H,t,$CH_2\underline{CH_3}$); 2.75(4H,m,CH_2CH_2); 3.0(4H,m, CH_2CH_2); 4.25(4H,q,$\underline{CH_2}CH_3$); 7.95(2H,pseudo-q,arom., J=9.0Hz,J=2.4Hz); 8.25(2H,d,arom.,J=2.4Hz); 8.60(2H,d, arom.,J=9.0Hz)
13	1770, 1730, 1665, 1630	1.25(9H,t,$CH_2\underline{CH_3}$); 2.84(6H,m,CH_2CH_2); 3.10(6H,m, CH_2CH_2); 4.28(6H,q,$\underline{CH_2}CH_3$); 8.05–8.65(5H,m,arom.)
14	1760, 1725, 1670, 1640	1.25(12H,t,$CH_2\underline{CH_3}$); 2.82(8H,m,CH_2CH_2); 3.08(8H,m, CH_2CH_2); 4.25(8H,q,$\underline{CH_2}CH_3$); 7.85–8.05(4H,m,arom.)

Pharmacological Results

Compounds **3–14** were tested in mice bearing Ehrlich ascites tumor cells (see Exp. Part). %T/C is reported in Table 1 only for compounds showing significant activity. No antitumor activity was found among the hydroxyalkylamino derivatives. The esters **10** and **12** proved active but no improvement was observed in comparison to the 1,8-disubstituted analog[1].

Experimental Part

A) *Chemistry*

MP: uncorr.; *TLC:* Bakerflex plates (silica-gel IB2-F). *Column chromatography:* Kieselgel 60 (Merck), activated at 120 °C for 2 h, in the proportion of 30 g per gram of substance; the eluent was a mixture of petroleum ether (bp 60–80°) acetone in various proportions. *IR-spectra:* (Nujol) Perkin-Elmer 298 spectrometer. *^{1}H-NMR spectra:* Varian XL-100, TMS int. stand.

Synthesis of compounds **3–9**

Compound **1** (5g, 18 mmoles) was dissolved in 30 ml pyridine and treated with the appropriate hydroxyalkylamine (300 mmoles). After 1 h reflux, the reaction mixture was poured onto ice and acidified with 6N-HCl. The precipitate was separated by column chromatography: unreacted 1,8-dichloroanthraquinone was the first compound obtained (5–10 %), then the monosubstituted derivatives were eluted (**4, 6, 8**: 35–45 %) and finally the disubstituted derivatives (**3, 5, 7, 9**: 35–45 %). See Tables 1, 2.

Synthesis of compounds **10–14**

The appropriate hydroxyanthraquinone (20 mmoles) was dissolved in pyridine and treated dropwise over 15 min with the calcd. amount of ethyl succinyl chloride. The reaction mixture was refluxed for 1 h, poured onto ice and acidified with 6N-HCl. The precipitate was crystallized with a yield of 50–80 %. See Tables 1,2.

B) *Pharmacology*

Eight female Swiss mice (average weight 21 ± 1 g) were implanted with 10^6 Ehrlich ascites tumor cells from donor mice. After 24 h the animals were treated i.p. with a single dose (200 mg/kg) of the compound under test (**3–14**) dissolved in DMSO: the amount of DMSO used was shown, in analogous experiments, not to affect tumor growth. If the dose proved toxic or active, the test was repeated at lower doses (100, 40 mg/kg) with other groups of eight mice (single dose treatment).

Another treatment was performed with three i.p. injections (100 mg/kg each) at the 2nd, 4th and 6th day after tumor implant (repeated dose treatment).

Deaths were recorded for the 60-day period. The activities were measured as the ratio of the mean survival time of the test animals to that of the control animals (ten mice) expressed as a percentage (%T/C). Significant activity is achieved with an increased life span of 25 % (T/C ≧ 125).

References

1 Part XIV: A. Andreani, M. Rambaldi, D. Bonazzi, G. Lelli, L. Greci, R. Bossa and I. Galatulas, Arch. Pharm. (Weinheim) *318,* 400 (1985).

2 R.K.Y. Zee-Cheng and C.C. Cheng, Drugs of the Future *8*, 229 (1983); Progr. Med. Chem. *20*, 83 (1983).
3 S.A. Islam, S. Neidle, B.M. Gandecha and J.R. Brown, Biochem. Pharmacol. *32*, 2801 (1983).
4 K.C. Murdock, U.S. 4389399; C.A. *99*, 139955c (1983).
5 K. Nakamura, T. Asai, T. Hara, N. Minorikawa and T. Suami, Bull. Chem. Soc. Jpn. *56*, 1812 (1983).
6 K.C. Murdock, EP85760; C.A. *99*, 194946a (1983).
7 M. Palumbo, C. Antonello, I. Viano, M. Santiano, O. Gia, S. Gastaldi and S. Marciani Magno, Chem. Biol. Interact. *44*, 207 (1983).
8 M. Palumbo and S. Marciani Magno, Int. J. Biol. Macromol. *5*, 301 (1983).
9 H.D. Hollis Showalter, J.L. Johnson, L.M. Werbel, W.R. Leopold, R.C. Jackson and E.F. Elslager, J. Med. Chem.*27*, 253 (1984).

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Untersuchungen an 1,3-Thiazinen, 26. Mitt.[1]

Neuartige N-Carbamoyl- und Thiocarbamoyl-2-thioxo-1,3-thiazinderivate

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Eingegangen am 25. Juni 1984

Die N-unsubstituierten 1,3-Thiazinderivate **1–3** werden durch Carbamoylchloride oder Thiocarbamoylchloride in Gegenwart von Triethylamin oder Natriumhydrid zu den N-Carbamoyl- bzw. N-Thiocarbamoyl-1,3-thiazinderivaten **5–9** umgesetzt.

1,3-Thiazines, XXVI[1]: Novel *N*-Carbamoyl- and Thiocarbamoyl-2-thioxo-1,3-thiazine Derivatives

The *N*-unsubstituted 1,3-thiazine derivatives **1–3** were transformed into the *N*-carbamoyl- or *N*-thiocarbamoyl-1,3-thiazine derivatives **5–9** by carbamic acid chlorides or thiocarbamic acid chlorides in the presence of triethylamine or sodium hydride.

In einigen vorangegangenen Mitt. haben wir über die N-Acylierung von N-unsubstituierten Tetrahydro- und Dihydro-1,3-thiazinen mit 2-Thioxo-, 2-Thioxo-4-oxo- oder 2,4-Dioxo-Struktur

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