

**1-SUBSTITUTION DERIVATIVES
OF 4-ARYL-2,3-DIBROMO-1-NAPHTHOL***

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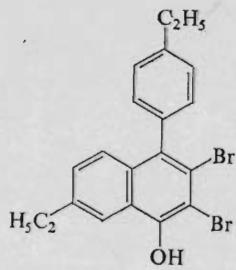
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Alkylation of 7-ethyl-4-(4-ethylphenyl)-2,3-dibromo-1-naphthol (*I*) with ethyl esters of ω -bromo-alkanoic acids *XX*–*XXIII* in a non-aqueous medium gave the 1-substitution derivatives *II*, *IV*, *VI* and *VIII* which were hydrolysed to the acids *III*, *V*, *VII* and *IX*. The acid *III* was used for syntheses of the esters *X*–*XIII* and amides *XIV*–*XVIII*. Compounds *II*–*XVIII* exhibited moderate antineoplastic effects in animals with transplanted tumours; best results were observed with the compound *II*.

In the preceding papers^{1–4} we have described syntheses of a number of 4-aryl-1-naphthol derivatives as model compounds structurally close to lignans of the podophyllin type. Some of these derivatives proved to exhibit moderate antineoplastic effects on transplanted tumours in experimental animals.

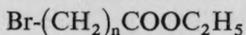
As a sequel of the study of derivatives of 4-aryl-1-naphthol, the present communication describes the syntheses of some 1-substitution derivatives of 7-ethyl-4-(4-ethylphenyl)-2,3-dibromo-1-naphthol (*I*) (compounds *II*–*XVIII*, Table I) and reports preliminary tests of selected compounds for antineoplastic efficacy in animals with transplanted tumours.



I

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Compounds *II*, *IV*, *VI* and *VIII* were obtained by alkylation of compound *I* with the corresponding ethyl esters of ω -bromoalkanoic acids *XX*–*XXIII* in the presence of sodium ethylate, adhering to the described procedures^{5,6}.



XX, *n* = 1; *XXI*, *n* = 3, *XXII*, *n* = 4, *XXIII*, *n* = 5

Attempted alkylation of compound *I* with ethyl 3-bromopropionate gave rise to only a trace amount of the alkylated product, as a consequence of dehydrohalogenation of the agent. The results were similar after alkylation in dimethylformamide, in the presence of anhydrous potassium carbonate or triethylamine.

Hydrolysis of compounds *II*, *IV*, *VI* and *VIII* in aqueous-alcoholic sodium hydroxide gave the respective ω -(7-ethyl-4-(4-ethylphenyl)-2,3-dibromo-1-naphthoxy) alkanoic acids *III*, *V*, *VIII* and *IX*. The acid *III* was used as the starting compound for synthesis of the esters *X*–*XIII* and amides *XIV*–*XVIII*. The esters and imides were obtained in good yields by the rewarding chloride method, consisting in reaction of 7-ethyl-4-(4-ethylphenyl)-2,3-dibromo-1-naphthoxyacetyl chloride (*XIX*), prepared *in situ* by treating compound *III* with thionyl chloride in an aromatic solvent, with an excess of an aliphatic alcohol or cyclopentyl alcohol, at the boiling temperature of the alcohol (compounds *X*–*XII*) or at 90°C (compound *XIII*). The amides *XV*–*XVIII* were prepared analogously by reaction of the chloride *XIX* with an excess of an aliphatic amine or cyclopentylamine in boiling benzene. To obtain the amide *XIV* we first introduced ammonia to a benzene solution of the compound *XIX*; after saturation the mixture was refluxed for 1 h.

Preliminary pharmacological tests have shown that the compounds *II*–*XVIII*, like the previously described compounds of this type, have a moderate antineoplastic effect on tumours transplanted on experimental animals. In the screening evaluation (for the method of testing and evaluation see refs^{7,8}) the most efficacious was the compound *II*. In the *p.o.* administration at the dosing of 100 mg/kg it exhibited a statistically significant reduction of the size of tumours S 180 by 35%, with no effect on the survival; tumours S 37 were diminished by 31%, the survival being extended by 27%. The same dosage extended the survival of animals with the Yoshida ascitic tumour by 39%. Compound *VIII*, administered *p.o.*, 100 mg/kg, extended the survival of animals with mammary adenocarcinoma HK by 36%. The acids *III*, *V*, *VII* and *IX* were less efficacious than their ethyl esters. In general, prolongation of the ethoxycarbonyl or the carboxyalkyl residue resulted in a decrease of efficacy. The esters *X*–*XIII*, derived from the acid *III*, had weaker antineoplastic effects than the ester *II*. Similar observations were made in evaluating the amides *XIV* to *XVIII*. These compounds exhibited some antineoplastic effects only in animals with mammary adenocarcinoma HK, where they extended the survival by 25–35% at the dosage of 100 mg/kg *p.o.*

EXPERIMENTAL

The melting points were determined on the Kofler block and are not corrected. The samples for elemental analyses were dried over phosphorus pentoxide at a pressure of 70 Pa and temperatures proportional to their melting points. Homogeneity of the samples and the reaction mixtures was followed by TLC on reflex foils Silufol UV 254 (Kavalíér) and by the quenching of UV light at 254 nm, an Universal UV-Lampe Camag (Muttenz-Schweiz) being used. The reaction mixtures were resolved by column chromatography on Kieselgel 60 reinst (Merck); the amounts of the Kieselgel in the columns corresponded to 30 fold weights of the chromatographed samples. $^1\text{H-NMR}$ spectra were measured in an apparatus Tesla BS487C (80 MHz), 10% solutions in CDCl_3 and tetramethylsilane as internal standard being used. IR spectra were recorded in a spectrometer Perkin-Elmer 577; 5% solutions in chloroform were employed.

Ethyl Esters of ω -(7-Ethyl-4-(4-ethylphenyl)-2,3-dibromo-1-naphthoxy)alkanoic Acids (*II, IV, VI, VIII*)

To a stirred solution of sodium (1.26 g, 5.5 mmol) in 300 ml of ethanol was added compound *I* (cf.¹) (21.7 g, 50 mmol) and the stirring was continued until it had dissolved. A corresponding ethyl ester (55 mmol) of ω -bromoalkanoic acid (esters *XX-XXIII*) was added to the solution and the mixture was refluxed for 3 h. After cooling and filtering off the separated sodium bromide the volatile components were distilled off *in vacuo*; the residue was dissolved in 250 ml of chloroform, shaken with two 50 ml portions of water, dried with anhydrous sodium sulphate and crystallized from a suitable solvent (compounds *II* and *IV*) or purified chromatographically using benzene-cyclohexane (1 : 1) as eluant (compounds *VI* and *VIII*). For yields see Table I.

Compound II: $^1\text{H-NMR}$ spectrum: δ 8.05 (bs, 1 H, H-8), 7.26, 7.02 (ABq, $J = 8.0$ Hz, 4 H, *p*-substituted Ar), 7.19 (bs, 2 H, H-5, H-6), 4.70 (s, 2 H, O—CH₂—CO), 4.30 (q, $J = 7.0$ Hz, 2 H, COO—CH₂), 2.73 (q, $J = 7.0$ Hz, 2 H, Ar—CH₂), 2.69 (q, $J = 7.0$ Hz, 2 H, Ar—CH₂), 1.31 (t, $J = 7.0$ Hz, 3 H, OCH₂—CH₃), 1.26 (t, $J = 7.0$ Hz, 3 H, ArCH₂—CH₃), 1.22 (t, $J = 7.0$ Hz, 3 H, ArCH₂—CH₃). IR spectrum: 1 745 (C=O, ester), 1 615, 1 550, 1 520 cm^{-1} (Ar).

Compound IV: $^1\text{H-NMR}$ spectrum: δ 7.90 (bs, 1 H, H-8), 7.25, 7.02 (ABq, $J = 8.0$ Hz, 4 H, *p*-substituted Ar), 7.18 (bs, 2 H, H-5, H-6), 4.13 (q, $J = 7.0$ Hz, 2 H, COO—CH₂), 4.10 (t, $J = 7.0$ Hz, 2 H, ArO—CH₂), 2.72 (q, $J = 7.0$ Hz, 2 H, Ar—CH₂), 2.69 (q, $J = 7.0$ Hz, 2 H, Ar—CH₂), 2.68 (t, $J = 7.0$ Hz, 2 H, CH₂—CO), 2.25 (m, 2 H, —CH₂—), 1.25 (t, $J = 7.0$ Hz, 3 H, COOCH₂—CH₃), 1.24 (t, $J = 7.0$ Hz, ArCH₂—CH₃), 1.20 (t, $J = 7.0$ Hz, 3 H, ArCH₂—CH₃). IR spectrum: 1 740 (C=O, ester), 1 618, 1 560, 1 520 cm^{-1} (Ar).

ω -(7-Ethyl-4-(4-ethylphenyl)-2,3-dibromo-1-naphthoxy)alkanoic Acids (*III, V, VII, IX*)

To a solution of 10 mmol of ethyl ester of an ω -(7-ethyl-4-(4-ethylphenyl)-2,3-dibromo-1-naphthoxy)alkanoic acid (*II, IV, VI, VIII*) in 50 ml of ethanol was added 50 ml of 10% sodium hydroxide. The mixture was refluxed for 1 h, concentrated to about 1/3 of the volume, diluted with 100 ml of water and brought to pH 2 with dilute hydrochloric acid (1 : 1). The separated compound was taken into three 30 ml portions of chloroform (or ether, in the case of compound *III*), the organic layers were washed with water, dried with anhydrous sodium sulphate and concentrated for crystallization. For yields see Table I.

Compound VII: $^1\text{H-NMR}$ spectrum: δ 10.80 (bs, 1 H, COOH), 7.90 (bs, 1 H, H-8), 7.25, 7.02 (ABq, $J = 8.0$ Hz, 4 H, *p*-substituted Ar), 7.18 (bs, 2 H, H-5, H-6), 4.10 (bt, 2 H, ArO—CH₂), 2.72 (q, $J = 7.0$ Hz, 2 H, Ar—CH₂), 2.69 (q, $J = 7.0$ Hz, 2 H, Ar—CH₂), 2.50 (bt, 2 H, CH₂—

—CO), 2.00 (bm, 4 H, 2 CH₂), 1.25 (t, $J = 7.0$ Hz, 3 H, ArCH₂—CH₃), 1.21 (t, $J = 7.0$ Hz, 3 H, ArCH₂—CH₃). IR spectrum: 2 600 (OH acid), 1 708 (CO acid), 1 618, 1 550, 1 520 cm⁻¹ (Ar).

Esters of 7-Ethyl-4-(4-ethylphenyl)-2,3-dibromo-1-naphthyoxyacetic Acid (X—XIII)

To chloride of the acid *XIX*, prepared from the acid *III* (9.84 g, 20 mmol) by its reaction with thionyl chloride (2.62 g, 22 mmol) in 50 ml of benzene containing 0.1 ml of dimethylformamide under reflux for 4 h (*cf.*¹), was added an excess of a corresponding alcohol (30—50 ml) and the mixture was refluxed for 3 h (compounds *X—XII*) or heated to 90°C for 4 h (compound *XIII*). After distilling off the volatile components the oily residue was dissolved in chloroform and shaken with a dilute solution (2—3%) of sodium hydrogen carbonate and water. The chloroform layer was dried and concentrated. The products, *X—XIII*, were recrystallized from methanol. For yield see Table I.

Compound X: ¹H-NMR spectrum: δ 8.00 (bs, 1 H, H-8), 7.25, 7.02 (Abq, $J = 8.0$ Hz, 4 H, *p*-substituted Ar), 7.19 (bs, 2 H, H-5, H-6), 4.70 (s, 2 H, O—CH₂—CO), 3.80 (s, 3 H, OCH₃), 2.73 (q, $J = 7.0$ Hz, 2 H, Ar—CH₂), 2.69 (q, $J = 7$ OHZ, 2 H, Ar—CH₂), 1.25 (t, $J = 7.0$ Hz, 3 H, ArCH₂—CH₃), 1.21 (t, $J = 7.0$ Hz, 3 H, ArCH₂—CH₃). IR spectrum: 1 745, (C=O ester), 1 620, 1 600, 1 550 cm⁻¹ (Ar).

Compound XI: ¹H-NMR spectrum: δ 8.04 (bs, 1 H, H-8), 7.26, 7.03 (ABq, $J = 8.0$ Hz, 4 H, *p*-substituted Ar), 7.20 (bs, 2 H, H-5, H-6), 5.25 (m, 1 H, COOCH), 4.70 (s, 2 H, O—CH₂CO), 2.73 (q, $J = 7.0$ Hz, 2 H, Ar—CH₂), 2.69 (g, $J = 7.0$ Hz, 2 H, Ar—CH₂), 1.38 (d, $J = 6.5$ Hz, 6 H, OCH—(CH₃)₂), 1.26 (t, $J = 7.0$ Hz, 3 H, ArCH₂—CH₃), 1.22 (t, $J = 7.0$ Hz, 3 H, ArCH₂—CH₃). IR spectrum: 1 745 (C=O ester), 1 620, 1 610, 1 545, 1 510 cm⁻¹ (Ar).

Compound XII: ¹H-NMR spectrum: δ 8.03 (bs, 1 H, H-8), 7.26, 7.03 (ABq, $J = 8.0$ Hz, 4 H, *p*-substituted Ar), 7.20 (bs, 2 H, H-5, H-6), 4.75 (s, 2 H, O—CH₂—CO), 4.30 (t, $J = 7.0$ Hz, 2 H, COO—CH₂), 2.74 (q, $J = 7.0$ Hz, 2 H, Ar—CH₂), 2.70 (q, $J = 7.0$ Hz, 2 H, Ar—CH₂), 1.65 (m, 4 H, 2 CH₂), 1.25 (t, $J = 7.0$ Hz, 3 H, ArCH₂—CH₃), 1.22 (t, $J = 7.0$ Hz, 3 H, ArCH₂—CH₃), 0.99 (bt, 3 H, (CH₂)₃—CH₃), IR spectrum: 1 745 (C=O ester), 1 620, 1 610, 1 540, 1 510 cm⁻¹ (Ar).

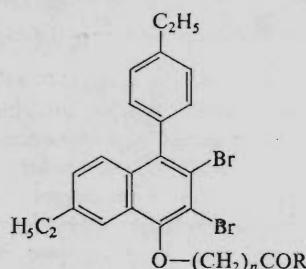
Compound XIII: ¹H-NMR spectrum: δ 8.04 (bs, 1 H, H-8), 7.26, 7.03 (ABq, $J = 8.0$ Hz, 4 H, *p*-substituted Ar), 7.20 (bs, 2 H, H-5, H-6), 5.36 (m, 1 H, COO—CH), 4.68 (s, 2 H, O—CH₂—CO), 2.74 (q, $J = 7.0$ Hz, 2 H, Ar—CH₂), 2.70 (q, $J = 7.0$ Hz, 2 H, Ar—CH₂), 1.40—2.20 (m, 8 H, cycl. CH₂), 1.26 (t, $J = 7.0$ Hz, 3 H, ArCH₂—CH₃), 1.22 (t, $J = 7.0$ Hz, 3 H, ArCH₂—CH₃). IR spectrum: 1 745 (C=O ester), 1 620, 1 550, 1 510 cm⁻¹ (Ar).

Amides of 7-Ethyl-4-(4-ethylphenyl)-2,3-dibromo-1-naphthyoxyacetic Acid (XIV—XVIII)

Chloride of the acid *XIX*, prepared from the acid *III* (9.84 g, 20 mmol) as described above, was freed from the acidic volatile components by distillation *in vacuo* and dissolved in 20 ml of benzene. With compound *XIV* the mixture was saturated with gaseous ammonia for 0.5 h, then heated to 65—70°C for 1 h. With compounds *XV—XVIII* an excess of a corresponding amine (3—5 ml) was added dropwise to a benzene solution of the acid *XIX* and the mixture was refluxed for 2 h. After removing the volatile components *in vacuo* the crude products were purified by crystallization from suitable solvents, given, along with the yields, in Table I.

Amide XIV: ¹H-NMR spectrum: δ 7.96 (bs, 1 H, H-8), 7.25, 7.02 (ABq, $J = 8.0$ Hz, 4 H, *p*-substituted Ar), 7.18 (bs, 2 H, H-5, H-6), 7.20, 6.60, (bss, 2 H, NH₂), 4.62, (s, 2 H, O—CH₂—CO), 2.74 (q, $J = 7.0$ Hz, 2 H, Ar—CH₂), 2.70 (q, $J = 7.0$ Hz, 2 H, Ar—CH₂), 1.26 (t, $J =$

TABLE I
1-Substitution derivatives of 4-aryl-2,3-dibromo-1-naphthol



Compound n	R (yield)	Formula (mol.mass)	M.p., °C (solvent)	Calculated/Found			
				% C	% H	% N	% Br
<i>II</i> 1	OC ₂ H ₅ (82.5)	C ₂₄ H ₂₄ Br ₂ O ₃ (520.3)	87-88 (hexane)	55.41	4.65	—	30.72
<i>III</i> 1	OH (70.1)	C ₂₂ H ₂₀ Br ₂ O ₃ (492.2)	184-185 (ethanol)	53.68	4.10	—	32.47
<i>IV</i> 3	OC ₂ H ₅ (76.6)	C ₂₆ H ₂₈ Br ₂ O ₃ (548.3)	79-81 (hexane)	56.95	5.15	—	29.15
<i>V</i> 3	OH (73.4)	C ₂₄ H ₂₄ Br ₂ O ₃ (520.3)	139-140 (benzene)	55.41	4.65	—	30.72
<i>VI</i> 4	OC ₂ H ₅ (86.0)	C ₂₇ H ₃₀ Br ₂ O ₃ (562.4)	^a	57.67	5.38	—	28.42
<i>VII</i> 4	OH (84.4)	C ₂₅ H ₂₆ Br ₂ O ₃ (534.3)	108-109 (benzene)	56.20	4.91	—	29.91
<i>VIII</i> 5	OC ₂ H ₅ (72.9)	C ₂₈ H ₃₂ Br ₂ O ₃ (576.4)	^b	58.35	5.59	—	27.73
<i>IX</i> 5	OH (70.1)	C ₂₆ H ₂₈ Br ₂ O ₃ (548.3)	126-127 (hexane)	56.95	5.15	—	29.15
<i>X</i> 1	OCH ₃ (78.0)	C ₂₃ H ₂₂ Br ₂ O ₃ (506.3)	87-88 (methanol)	54.57	4.38	—	31.57
<i>XI</i> 1	OCH(CH ₃) ₂ (73.9)	C ₂₅ H ₂₆ Br ₂ O ₃ (534.3)	87-89 (methanol)	54.79	4.43	—	31.55
<i>XII</i> 1	OCH ₂ CH ₂ CH ₂ CH ₃ (75.7)	C ₂₆ H ₂₈ Br ₂ O ₃ (548.3)	85-87 (methanol)	56.22	5.07	—	29.91
<i>XIII</i> 1	O-C ₅ H ₉ -cyclo (41.0)	C ₂₇ H ₂₄ Br ₂ O ₃ (560.4)	76-78 (methanol)	56.22	5.07	—	29.81
				56.88	5.17	—	28.86
				57.87	5.03	—	28.57
				57.96	4.69	—	28.70

TABLE I
(Continued)

Compound n	R yield	Formula (mol.mass)	M.p., °C (solvent)	Calculated/Found			
				% C	% H	% N	% Br
XIV 1	NH ₂ (64.6)	C ₂₂ H ₂₁ Br ₂ NO ₂ (491.2)	202–204 (chloroform)	53.78 54.00	4.00 4.25	2.85 2.95	32.56 32.70
XV 1	N(C ₂ H ₅) ₂ (73.4)	C ₂₆ H ₂₉ Br ₂ NO ₂ (547.4)	102–104 (chloroform)	57.05 57.09	5.34 5.74	2.56 2.35	29.20 29.55
XVI 1	NHCH ₂ CH ₂ CH ₂ CH ₃ (40.6)	C ₂₆ H ₂₉ Br ₂ NO ₂ (547.4)	120–122 (chloroform)	57.05 57.22	5.34 5.19	2.56 2.31	29.20 28.95
XVII 1	NHCH ₂ CH(CH ₃) ₂ (55.0)	C ₂₆ H ₂₉ Br ₂ NO ₂ (547.4)	139–141 (chloroform)	57.05 57.33	5.34 5.42	2.56 2.66	29.20 28.91
XVIII 1	NH—C ₅ H ₉ -cyclo (40.7)	C ₂₇ H ₂₉ Br ₂ NO ₂ (559.4)	156–158 (chloroform)	57.98 58.33	5.23 5.24	2.50 2.25	28.57 28.63

^a $n_D^{20} = 1.5769$; ^b $n_D^{20} = 1.5958$.

= 7.0 Hz, 3 H, ArCH₂—CH₃). IR spectrum: 3 520, 3 400 (NH₂); 1 690 (C=O amide, 1 620, 1 520 cm⁻¹ (Ar).

Amide XVI: ¹H-NMR spectrum: δ 7.88 (bs, 1 H, H-8), 7.27, 7.04 (ABq, $J = 8.0$ Hz, 4 H, *p*-substituted Ar), 7.20 (bs, 2 H, H-5, H-6), 7.10 (bd, 1 H, CO—NH), 4.60 (s, 2 H, O—CH₂—CO), 3.50 (m, 2 H, NH—CH₂), 2.75 (bq, $J = 7.0$ Hz, 4 H, N—CH₂) 1.50 (m, 4 H, 2 CH₂), 1.28 (t, $J = 7.0$ Hz, 3 H, ArCH₂—CH₃), 1.25 (t, $J = 7.0$ Hz, 3 H, (ArCH₂—CH₃), 0.99 (bt, 3 H, (CH₂)₃—CH₃). IR spectrum: 3 420 (NH), 1 670 (C=O amide), 1 620, 1 520 cm⁻¹ (Ar).

Amide XVII: IR spectrum: 3 420 (NH), 1 670 (CO amide), 1 620, 1 520 cm⁻¹ (Ar).

Amide XVIII: ¹H-NMR spectrum: δ 7.86 (s, 1 H, H-8), 7.26, 7.04 (ABq, $J = 8.0$ Hz, 4 H, *p*-substituted Ar), 7.20 (bs, 2 H, H-5, H-6), 7.10 (bd, 1 H, CO—NH), 4.58 (s, 2 H, O—CH₂—CO), 4.42 (m, 1 H, CONH—CH), 2.74 (bq, $J = 7.0$ Hz, 4 H, Ar—CH₂), 1.50–2.20 (m, 8 H, cycl. CH₂), 1.28 (t, $J = 7.0$ Hz, 3 H, ArCH₂—CH₃), 1.25 (t, $J = 7.0$ Hz, 3 H, ArCH₂—CH₃). IR spectrum: 3 420 (NH), 1 665 (CO amide), 1 620, 1 520 cm⁻¹ (Ar).

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