DERIVATIVES OF 4-ARYL-2,3-DIHALOGENO-1-NAPHTHOL*

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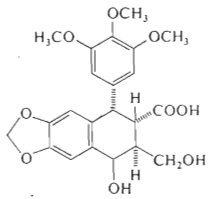
Using intramolecular cyclization of the *in situ* prepared chlorides of acids *XVI—XX*, catalysed with zinc chloride, corresponding 4-aryl-2,3-dihalogeno-1-naphthols *III—VII* were prepared. Methylation or acetylation of compounds *I*, *IV—VI* gave O-methyl derivatives *VIII—XI* or O-acetyl derivatives *XII—XV*, respectively. Compounds *III—XV* displayed a weak antineoplastic effect in animals with some transplantable tumours.

In our preceding paper[1] we described the synthesis of 7-ethyl-4-(4-ethylphenyl)--2,3-dibromo-1-naphthol (*I*), a compound derived from the antineoplastic preparation Edikron[2]. The structure of compound *I* (ref.[1]) seemed to be prospective for chemical modifications, especially from the point of view of the synthesis of simple model substances, structurally related to podophylic acid (*II*) or its biologically active derivatives obtained semisynthetically from natural sources (*Podophyllum peltatum*), among which, for example, the preparations SPG, SPI and also VM-26 and VP-16 are used in the chemotherapy of cancer[3-5].



II

In this communication we concentrated on the synthesis of further 4-aryl derivatives of 2,3-dihalogeno-1-naphthols *III – VII* and their derivatives, prepared on substitution of the hydrogen atom in the aromatic hydroxyl group by the methyl group (*VIII – XI*), or the acetyl group (*XII – XV*) (Table I).

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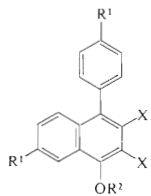
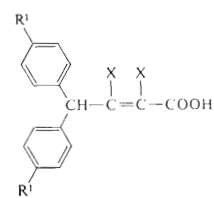
The derivatives of 1-naphthol *III*–*VII* were synthetized from corresponding 4,4-diaryl-2,3-dihalogeno-2-butenoic acids *XVI*–*XX* (ref.[2]) using the procedure described[1] for the preparation of compound *I*, and also by cyclization catalyzed with zinc chloride or its mixture with phosphorus pentoxide, both in melt (*IV*–*VI*) and in dichloroethane (*III* and *VII*). Cyclization with zinc chloride in dichloroethane



III–*XV*
I; $R^1 = C_2H_5$, X = Br
R^2 = H



XVI; R^1 = H; X = Cl
XVII; R^1 = H; X = Br
XVIII; $R^1 = CH_3$; X = Br
XIX; $R^1 = C_2H_5$; X = Cl
XX; R^1 = Cl; X = Cl

was used when the reactive chloride of acid *XVI* and *XX* would not form a homogeneous melt with zinc chloride. As is evident from Table I the cyclization procedure in organic solvent is less favourable from the point of view of the yield. When compounds *I*, *IV*–*VI* were treated with dimethyl sulfate in aqueous alkaline medium corresponding O-methyl derivatives *VIII*–*IX* were obtained. Compound *IX* was also prepared on methylation of compound *V* with diazomethane. Similarly, on acetylation of compounds *I*, *IV*–*VI* with acetyl chloride or acetic anhydride in pyridine compounds *XII*–*XV* were obtained. The structure of selected compounds was confirmed by ^{1}H-NMR and IR spectra.

In preliminary biological testing compounds *III*–*XV* showed a mild antineoplastic effect in animals with transplantable tumours, which, however, did not attain the effect of the starting 4,4-diaryl-2,3-dihalogeno-2-butenoic acids *XVI*–*XX* or of compound *I*. The effect of the compounds was manifested by a 20–25% diminution of the tumour size in experimental animals when doses of 50–100 mg/kg were applied *p.o.* More detailed data on this evaluation will be published elsewhere.

EXPERIMENTAL

The melting points were determined on a Kofler block and they are not corrected. Samples for elemental analysis were dried at temperatures corresponding to their melting points over phosphorus pentoxide at 70 Pa vacuum. The homogeneity of the samples and the composition of the

reaction mixtures was checked by TLC on Silufol foils UV_{254} (Kavalier), using UV light of 254 nm wavelength for detection. The ^{1}H-NMR spectra of selected compounds were measured on a spectrometer Tesla BS487C (80 MHz) in 10% solution in deuteriochloroform, using tetramethylsilane as internal reference. The IR spectra were taken on an Infrascan (Hilger) spectrometer in 5% solution in chloroform, in a 0·1 mm KBr cell.

TABLE I

Derivatives of 4-Aryl-2,3-dihalogeno-1-naphthol *III*—*XV*

Compound Halogen	R^1 R^2	Formula (mol. mass)	M.p., °C (solvent)	Yield %	Calculated/Found % C	% H	% Cl(Br)
III	H	$C_{16}H_{10}Cl_2O$	104—105	13·4	66·45	3·48	24·52
Cl	H	(289·2)	(hexane)		66·78	3·64	24·35
IV	H	$C_{16}H_{10}Br_2O$	133—135	79·9	50·83	2·67	(42·27)
Br	H	(378·1)	(chloroform)		51·11	2·79	(42·31)
V	CH_3	$C_{18}H_{14}Br_2O$	176—177	53·4	53·23	3·47	(39·35)
Br	H	(406·1)	(hexane)		53·33	3·55	(39·62)
VI	C_2H_5	$C_{20}H_{18}Cl_2O$	131—133	56·5	69·58	5·25	20·54
Cl	H	(345·3)	(ethanol)		69·48	5·48	20·68
VII	Cl	$C_{16}H_8Cl_4O$	158—159	16·8	53·67	2·25	39·61
Cl	H	(358·1)	(hexane)		53·63	2·30	39·39
VIII	H	$C_{17}H_{12}Br_2O$	99—102	92·0	52·07	3·09	(40·75)
Br	CH_3	(392·1)	(chloroform)		52·19	3·19	(40·65)
IX	CH_3	$C_{19}H_{16}Br_2O$	98—99	83·8	54·31	3·84	(38·04)
Br	CH_3	(420·2)	(heptane)		54·52	3·96	(38·05)
X	C_2H_5	$C_{21}H_{20}Cl_2O$	87—88	77·6	70·19	5·62	19·74
Cl	CH_3	(359·3)	(benzene)		70·28	5·68	19·51
XI	C_2H_5	$C_{21}H_{20}Br_2O$	82—83	89·0	56·28	4·48	(35·60)
Br	CH_3	(448·2)	(hexane)		56·53	4·59	(35·54)
XII	H	$C_{18}H_{12}Br_2O_2$	153—154	97·5	51·46	2·87	(38·05)
Br	CH_3CO	(420·1)	(chloroform)		51·34	2·98	(38·34)
XIII	CH_3	$C_{20}H_{16}Br_2O_2$	161—162	54·5	53·59	3·59	(35·65)
Br	CH_3CO	(448·2)	(ethanol)		53·89	3·74	(35·90)
XIV	C_2H_5	$C_{22}H_{20}Cl_2O_2$	104—106	80·3	68·22	5·21	18·31
Cl	CH_3CO	(387·3)	(ethanol)		68·40	5·45	18·48
XV	C_2H_5	$C_{22}H_{20}Br_2O_2$	121—125	78·7	55·40	4·23	(33·56)
Br	CH_3CO	(476·2)	(chloroform)		55·42	4·05	(33·77)

Cyclization of 4,4-Diaryl-2,3-dihalogeno-2-butenoic Acids

Anhydrous zinc chloride (1·0—1·5 molar equivalents) or its mixture with 10—15% (by weight) of phosphorus pentoxide was added to the reaction product of acids *XVI*—*XX* with 1·1 molar equivalents of thionyl chloride, prepared in an inert solvent according to ref.[6], and cyclization was carried out in the following manner: (Method *A*), in melt, by stirring at 60°C and, when the reaction set on, at 80°C for 2 h. The mixture was decomposed with water, the organic product was extracted with chloroform and the crude product purified by crystallization from a suitable solvent. (Method *B*), in an inert solvent, at boiling temperature, for 30 min up to 3 h. After the decomposition of the mixture the product was separated from the starting substance by chromatography on Kieselgel 60 (Merck), using benzene for elution. For yields of the reactions and the melting points see Table I.

4-*Phenyl*-2,3-*dichloro*-1-*naphthol* (III). Method *B*: 3·07 g (10 mmol) of acid *XVI* was cyclized using 2·04 g (15 mmol) of zinc chloride in 25 ml od dichloroethane and refluxing for 30 min. ^{1}H-NMR spectrum: δ 8·20 (m, 1 H, 8-H), 7·10—7·60 (m, 8 H, Ar—H), 6·15 (s, 1 H, OH). IR spectrum: 3 540 (phenol OH), 1 590, 1 510, 880 cm^{-1} (Ar).

4-*Phenyl*-2,3-*dibromo*-1-*naphthol* (IV). Method *A*: 396 g (1 mol) of acid *XVII* was cyclized using 204 g (1·5 mol) of zinc chloride and 20 g of phosphorus pentoxide. ^{1}H-NMR spectrum: δ 8·22 (m, 1 H, 8-H), 7·10—7·60 (m, 8 H, Ar—H), 6·15 (s, 1 H, OH). IR spectrum: 3 500 (phenolic OH), 1 580, 1 570, 1 500 (Ar), 1 150 cm^{-1} (Ar—O—H).

7-*Methyl*-4-(4-*methylphenyl*)-2,3-*dibromo*-1-*naphthol* (V). Method *A*: 4·24 g (10 mmol) of acid *XVIII*, cyclization with 2·04 g (15 mmol) of zinc chloride and 0·2 g of phosphorus pentoxide. ^{1}H-NMR spectrum: δ 8·01 (bs, 1 H, 8-H), 7·0—7·40 (m, 6 H, Ar—H), 6·11 (s, 1 H, OH), 2·51 (bs, 3 H, Ar—CH_3), 2·49 (bs, 3 H, ArCH_3). IR spectrum: 3 500 (phenolic OH), 1 565, 1 510 (Ar) cm^{-1}.

7-*Ethyl*-4-(4-*ethylphenyl*)-2,3-*dichloro*-1-*naphthol* (VI). Method *A*: 72·6 g (0·2 mol) of acid *XIX*, cyclization with 40·8 g (0·3 mol) of zinc chloride and 4 g of phosphorus pentoxide at 80°C for 2 h and at 90°C for another hour. ^{1}H-NMR spectrum: δ 7·95 (bs, 1 H, 8-H), 7·00—7·40 (m, 6 H, Ar—H), 6·10 (s, 1 H, OH), 2·75 (q, J = 7·0 Hz, 2 H, Ar—CH_2), 2·72 (q, J = 7·0 Hz, 2 H, Ar—CH_2), 1·29 (t, J = 7·0 Hz, 3 H, ArCH_2—CH_3), 1·26 (t, J = 7·0 Hz, 3 H, ArCH_2—CH_3).

7-*Chloro*-4-(4-*chlorophenyl*)-2,3-*dichloro*-1-*naphthol* (VII). Method *B*: 3·76 g (10 mmol) of acid *XX*, cyclization with 1·36 g (10 mmol) of zinc chloride and 0·2 g of phosphorus pentoxide in 25 ml of dichloroethane, 3 h refluxing. ^{1}H-NMR spectrum: δ 8·15 (bs, 1 H, 8-H), 7·45, 7·13 (ABq, J = 8·5 Hz, 4 H, *p*-substituted Ar), 7·20 (m, 2 H, Ar—H), 6·15 (s, 1 H, OH). IR spectrum: 3 510 (phenol OH), 1 610, 1 598, 1 571 (Ar), 920, 882 cm^{-1} (Ar—H).

Methylation of Derivatives of 2,3-Dihalogeno-1-naphthol

One equivalent of a derivative of 2,3-dihalogeno-1-naphthol *I*, *IV*—*VI* was introduced gradually into a stirred aqueous solution of sodium hydroxide (1·2—1·4 molar equivalents). Dimethyl sulfate (1·3 molar equivalents) was then added to the solution formed and the mixture was heated at 80°C for 1·5 h. The separated product was dissolved in chloroform and the chloroform solution was washed with 2% potassium hydroxide solution and water, then dried and concentrated to crystallization.

4-*Phenyl*-2,3-*dibromo*-1-*methoxynaphthalene* (VIII): 3·78 g (10 mmol) of compound *IV*, 0·55 g (13·8 mmol) of sodium hydroxide in 7 ml of water and 1·26 ml of dimethyl sulfate. ^{1}H-NMR spectrum: δ 8·14 (m, 1 H, 8-H), 7·10—7·70 (m, 8 H, ArH), 4·05 (s, 3 H, ArOCH_3).

7-*Methyl*-4-(4-*methylphenyl*)-2,3-*dibromo*-1-*methoxynaphthalene* (IX): 4·06 g (10 mmol) of compound *V*, 0·55 g (13·8 mmol) of sodium hydroxide in 10 ml of water, 1·26 g of dimethyl sulfate, reaction time 1 h. ^{1}H-NMR spectrum: δ 7·90 (m, 1 H, 8-H), 7·00—7·50 (m, 6 H, ArH), 4·00 (s, 3 H, $ArOCH_3$), 2·50 (bs, 3 H, $ArCH_3$), 2·45 (bs, 3 H, $ArCH_3$). IR spectrum: 1 625, 1 550, 1 525 (Ar), 830 cm^{-1} (*p*-substituted Ar—H).

7-*Ethyl*-4-(4-*ethylphenyl*)-2,3-*dichloro*-1-*methoxynaphthalene* (X): 6·9 g (20 mmol) of compound *VI*, 1·12 g (28 mmol) of sodium hydroxide in 20 ml of water, 2·6 ml of dimethyl sulfate, 1·5 h at 90°C. ^{1}H-NMR spectrum: δ 7·85 (bs, 1 H, 8-H), 7·00—7·40 (m, 6 H, ArH), 4·00 (s, 3 H, $Ar—OCH_3$), 3·75 (q, J = 7·0 Hz, 2 H, $ArCH_2$), 3·71 (q, J = 7·0 Hz, 2 H, $ArCH_2$), 1·31 (t, J = = 7·0 Hz, 3 H, $ArCH_2—CH_3$), 1·28 (t, J = 7·0 Hz, 3 H, $ArCH_2—CH_3$). IR spectrum: 1 620, 1 650 (Ar), 825 cm^{-1} (*p*-substituted Ar—H).

7-*Ethyl*-4-(4-*ethylphenyl*)-2,3-*dibromo*-1-*methoxynaphthalene* (XI): 175 g (0·4 mol) of compound *I* (ref.[1]), 22·3 g (0·55 mol) of sodium hydroxide in 280 ml of water, 50·7 ml of dimethyl sulfate, 1 h at 80°C.

7-Methyl-4-(4-methylphenyl)-2,3-dibromo-1-methoxynaphthalene (*IX*)

Diazomethane (1·3 g, 30 mmol) in 200 ml of ether was added to a solution of 3·5 g (8·6 mmol) of compound *V* in 50 ml of ether, cooled at 0°C. The mixture was allowed to stand at 20—25°C for 24 h and evaporated. Crystallization of the residue from hexane gave 2·32 g (60%) of compound *IX*, m.p. 98—99°C. ^{1}H-NMR spectrum: δ 7·88 (bs, 1 H, 8-H) 7·00—7·40 (m, 6 H, ArH), 4·00 (s, 3 H, $Ar—OCH_3$), 2·48 (bs, 3 H, $Ar—CH_3$), 2·43 (bs, 3 H, $Ar—CH_3$).

Acetylation of Derivatives of 2,3-Dihalogeno-1-naphthol

Acetyl chloride or acetic anhydride was added gradually to a cooled solution (0°C) of derivative of 2,3-dihalogeno-1-naphthol in pyridine or a mixture of pyridine and chloroform and the mixture was stirred at 0°C for half-an-hour and heated at 100°C for 2 h. After evaporation of the volatile components the residue was dissolved in chloroform, the solution washed with 5% HCl and water, and concentrated to crystallization.

4-*Phenyl*-2,3-*dibromo*-*acetoxynaphthalene* (XII) (3·78 g; 10 mmol) of compound *IV* were dissolved in 9 ml of pyridine and 10 ml of chloroform and 1·64 g (20 mmol) of acetyl chloride were added to it. ^{1}H-NMR spectrum: δ 7·85 (m, 1 H, 8-H), 7·10—7·60 (m, 8 H, Ar—H), 2·55 (s, 3 H, $COCH_3$). IR spectrum: 1 775 ($ArOCOCH_3$), 1 610, 1 560, 1 510 cm^{-1} (Ar).

7-*Methyl*-4-(4-*methylphenyl*)-2,3-*dibromo*-1-*acetoxynaphthalene* (XIII): 1·0 g (2·46 mmol) of compound *V* was dissolved in 25 ml of pyridine and 1 ml of acetic anhydride was added and the mixture heated at 80°C for 1 h.

7-*Ethyl*-4-(4-*ethylphenyl*)-2,3-*dichloro*-1-*acetoxynaphthalene* (XIV): 6·9 g (20 mmol) of compound *VI* in 15 ml of pyridine and 18 ml of chloroform were additioned with 3·14 g (40 mmol) of acetyl chloride and refluxed for 2 h. ^{1}H-NMR spectrum: δ 7·50 (bs, 1 H, 8-H), 7·00—7·40 (m, 6 H, Ar—H), 2·72 (q, J = 7·0 Hz, 4 H, 2 $ArCH_2$), 2·49 (s, 3 H, $COCH_3$), 1·29 (t, J = 7·0 Hz, 3 H, $ArCH_2—CH_3$), 1·23 (t, J = 7·0 Hz, 3 H, $ArCH_2—CH_3$). IR spectrum: 1 772 ($ArOCOCH_3$), 1 620, 1 570 (Ar), 880, 830 cm^{-1} (Ar—H).

7-*Ethyl*-4-(4-*ethylphenyl*)-2,3-*dibromo*-I-*acetoxynaphthalene* (XV): 110 g (0·25 mol) of compound *I* (ref.[1]) in 220 ml of pyridine and 300 ml of chloroform were additioned with 41 g (0·52 mol) of acetyl chloride and refluxed for 3 h.

Biological testing of the substances for their antineoplastic effect was carried out by Dr K. Řežábek and his coworkers of the department of pharmacology and the analyses by Mrs J. Komancová of the analytical department of our Institute.

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