HYDROLYTIC PRODUCTS OF 4-ARYL-2,3-DICYANO-1-NAPHTHOL DERIVATIVES*

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Depending on the conditions of hydrolysis, vicinal aromatic dicyano derivatives *Ia—Ic* gave anhydrides *IIa—IIe* and imides of 4-aryl-1-alkoxynaphthalene-2,3-dicarboxylic acids, *IIIa,b*, along with products of partial hydrolysis, decarboxylation and demethylation, *IVa—IVd*, *IVf—IVg*, and derivatives of benzo(*c*)fluorene, *Va—Vc*. The derivatives *Va—Vc* were also obtained by acid hydrolysis of dicyano derivatives *Id—g*. Methanolysis of the anhydride *IId* gave a mixture of positional isomers, *IVh*, which was esterified to the diester *IVe*. Intramolecular ring closure of the isomers *IVh* afforded derivatives of benzo(*c*)fluorene, *VIa—VIb*. The structures of the selected compounds were corroborated by IR and ^{1}H-NMR spectra. The compounds *Va—Vc* exhibited antiviral effects and interferonogenic activities *in vivo*.

With a view to synthetizing compounds possibly having antineoplastic effects, we have described syntheses of 2,3-disubstitution derivatives of 4-aryl-1-naphthol[1-3], and made use of their structural similarities to podophyllotoxin type lignans and their ready accessibility for syntheses of model compounds and study of their biological effects.

The present communication describes procedures used for hydrolysis of 4-aryl-2,3-dicyano-1-naphthol derivatives[3] (*Ia—Ig*) and the products obtained under different hydrolytic conditions (Table I). These conditions were so chosen as to produce the corresponding derivatives of 4-aryl-2,3-naphthalenedicarboxylic acids, with the view of employing the latter for syntheses of simple models of the podophyllic acid type: *a*) aqueous–ethanolic medium of potassium hydroxide (method *A*), *b*) potassium hydroxide in ethylene glycol (method *B*) and *c*) dilute sulphuric acid in acetic acid (method *C*). The methods were first tested on the compound *Ic*, and after assessing the courses of hydrolysis a suited procedure was applied to other compounds.

Hydrolysis of *Ic* by method *A* produced a mixture from which *IIc* and *IIIb* were isolated as the main constituents; further isolated were small amounts of the demethylation product of the starting compound, *Ig*, and product *IVf*. Under the given hydrolytic conditions we observed, and demonstrated spectrometrically,

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TABLE I

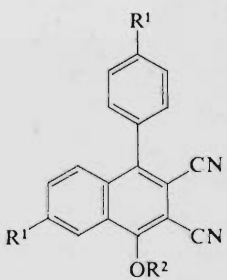
Hydrolytic products of some derivatives of 4-aryl-2,3-dicyano-1-naphthol

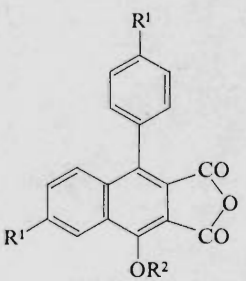
Compound	R^1 R^2	X^1 X^2	Formula (mol.mass)	M.p., °C (solvent)	Calculated/Found % C	% H	% N
IIa	H	—	$C_{19}H_{12}O_4$	201—203	75·00	3·97	—
	CH_3	—	(304·3)	(chloroform)	74·79	3·96	—
IIb	CH_3	—	$C_{21}H_{16}O_4$	159—162	75·90	4·85	—
	CH_3	—	(332·4)	(methanol)	75·66	5·08	—
IIc	C_2H_5	—	$C_{24}H_{22}O_4$	113—114	76·98	5·92	—
	C_2H_5	—	(374·4)	(ethanol)	77·07	5·97	—
IId	C_2H_5	—	$C_{23}H_{20}O_4$	138—139	76·65	5·60	—
	CH_3	—	(360·4)	(chloroform)	76·90	5·79	—
IIe	H	—	$C_{20}H_{14}O_4$	198—201	75·46	4·43	—
	C_2H_5	—	(318·4)	(chloroform)	75·55	4·47	—
IIIa	H	—	$C_{20}H_{15}NO_3$	240—241	75·70	4·76	4·41
	—	—	(317·3)	(chloroform–methanol)	75·74	4·66	4·51
IIIb	C_2H_5	—	$C_{24}H_{23}NO_3$	169—170	77·19	6·21	3·75
	—	—	(373·5)	(methanol)	77·23	6·01	3·94
IVa	C_2H_5	H	$C_{21}H_{20}O_3$	226—228	78·73	6·92	—
	H	COOH	(320·4)	(acetone)	78·79	6·53	—
IVb	C_2H_5	COOH	$C_{21}H_{20}O_3$	149—150	78·73	6·92	—
	H	H	(320·4)	(chloroform)	78·84	6·50	—
IVc	C_2H_5	$CONH_2$	$C_{21}H_{21}NO_2$	210—214	78·97	6·63	4·38
	H	H	(319·4)	(acetone)	78·96	6·88	4·18
IVd	C_2H_5	$COOCH_3$	$C_{22}H_{22}O_3$	128—129	79·02	6·63	—
	H	H	(334·4)	(hexane)	79·12	6·71	—
IVe	C_2H_5	$COOCH_3$	$C_{25}H_{26}O_5$	83—84	73·87	6·45	—
	CH_3	$COOCH_3$	(406·5)	(hexane)	73·67	6·61	—
IVf	C_2H_5	COOH	$C_{25}H_{26}O_5$	162—164	73·87	6·45	—
	C_2H_5	$COOCH_3$	(406·5)	(benzene)	73·72	6·42	—
IVg	H	$CONH_2$	$C_{17}H_{13}NO_2$	266—268	77·54	4·97	5·31
	H	H	(263·3)	(chloroform)	77·47	4·80	5·12
IVh[a]	C_2H_5	COOH	$C_{24}H_{24}O_5$	173—175	73·45	6·16	—
	CH_3	$COOCH_3$	(392·4)	(chloroform–hexane)	73·65	6·27	—
Va	H	—	$C_{17}H_{10}O_2$	255—257[b]	82·91	4·09	—
	—	—	(246·3)	(acetone)	82·47	4·15	—

TABLE I
(*Continued*)

Compound	R^1 R^2	X^1 X^2	Formula (mol.mass)	M.p., °C (solvent)	Calculated/Found % C	% H	% N
Vb	CH_3	—	$C_{19}H_{14}O_2$	260 subl.	83·19	5·14	—
	—	—	(274·3)	(chloroform)	82·85	5·39	—
Vc	C_2H_5	—	$C_{21}H_{18}O_2$	255—257	83·42	5·99	—
	—	—	(302·4)	(chloroform)	83·12	6·01	—
VIa	H	—	$C_{23}H_{20}O_4$	130—132	76·64	5·59	—
	—	—	(360·4)	(methanol)	76·47	5·89	—
VIb	CH_3	—	$C_{24}H_{22}O_4$	115—116	76·98	5·92	—
	—	—	(374·4)	(methanol)	76·77	6·18	—

[a] Mixture of positional isomers; [b] reported[5] m.p. above 235°C.



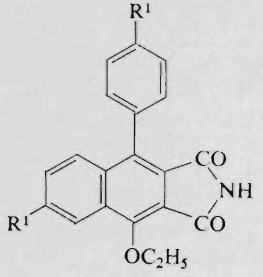


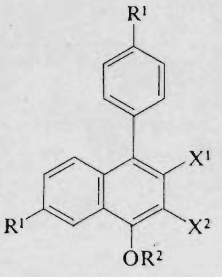
Ia, $R^1 = H$, $R^2 = CH_3$
Ib, $R^1 = R^2 = CH_3$
Ic, $R^1 = C_2H_5$, $R^2 = CH_3$
Id, $R^1 = C_2H_5$, $R^2 = COCH_3$
Ie, $R^1 = R^2 = H$
If, $R^1 = CH_3$, $R^2 = H$
Ig, $R^1 = C_2H_5$, $R^2 = H$

IIa, $R^1 = H$, $R^2 = CH_3$
IIb, $R^1 = R^2 = CH_3$
IIc, $R^1 = R^2 = C_2H_5$
IId, $R^1 = C_2H_5$, $R^2 = CH_3$
IIe, $R^1 = H$, $R^2 = C_2H_5$

a transetherification replacement of the 1-methoxy group by a 1-ethoxy group, proceeding probably by a mechanism analogous to that described by Schmidhammer and coworkers[4]. The formation of the methyl ester *IVf* in the ethanolic medium can be ascribed to the participation of methanol, released by the transetherification, in the sequence of the reactions. The identity of the compound *IVf* was corroborated by spectral data. Using an analogous procedure, the compound *Ia* was converted

into the corresponding anhydride *IIe* and imide *IIIa*. With method *B* applied on the compound *Ic* we isolated, from the reaction mixture, products of demethylation and partial decarboxylation, *IVa,b*, or partial hydrolysis, *IVc*. The compound *IVb*,





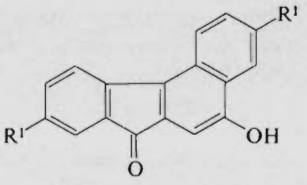
IIIa, $R^1 = H$
IIIb, $R^1 = C_2H_5$

IVa–IVf, $R^1 = C_2H_5$
IVa, $R^2 = X^1 = H$, $X^2 = COOH$
IVb, $R^2 = X^2 = H$, $X^1 = COOH$
IVc, $R^2 = X^2 = H$, $X^1 = CONH_2$
IVd, $R^2 = X^2 = H$, $X^1 = COOCH_3$
IVe, $R^2 = CH_3$, $X^1 = X^2 = COOCH_3$
IVf, $R^2 = C_2H_5$, $X^1 = COOH$, $X^2 = COOCH_3$
IVg, $R^1 = R^2 = X^2 = H$, $X^1 = CONH_2$
IVh, $R^1 = C_2H_5$, $R^2 = CH_3$, $X^1, X^2 = COOH$, $COOCH_3$

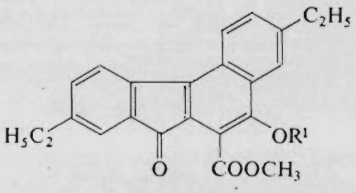
arising as the main product, was also characterised in the form of its methyl ester, *IVd*. With method *C* the compound *Ic* hydrolysed to the anhydride *IId* and 3,9-diethyl-5-hydroxy-7-oxo-7*H*benzo(*c*) fluorene, *Vc*, the latter being produced by ring closure of the transiently formed derivative of the carboxylic acid. Some coloured sulphonation products, not further identified, were also obtained. The proportion of the compounds *IId* and *Vc* depended on the conditions employed (ratio of the components, temperature, reaction time). However, the reaction course was never "homogeneous" in respect of the final product. To verify the reaction course the anhydride *IIc* was subjected to ring closure in the conditions of method *C* and, in keeping with the afore-said assumptions, the compound *Vc* was obtained.

Out of the three procedures of hydrolysis, the best one proved to be method *C*, which gave good yields of the compound *IId*. This method was also used to hydrolyse the dicyano derivatives *Ia* and *Ib*. Analogously we isolated the corresponding anhydrides *IIa* and *IIb*, along with the derivatives of benzo(*c*)fluorene, *Va* (ref.[5]) and *Vb*. In hydrolysis of the compound *Ia* we succeeded in isolation of the compound *IVg*, formed as a trace by-product. Applying method *C* to the compounds *Ie–g* we prepared the compounds *Va–c* as the main products. Similarly, the compound *Id*, having a labile ester function in position 1, afforded the compound *Vc*.

Methanolysis of the compound *IId* gave the ester-acid *IVh*, as a mixture of the positional isomers in the proportion 1 : 1 (see the ^{1}H-NMR spectrum), which was esterified with methanol in the presence of sulphuric acid to the diester *IVe*, a small amount of the anhydride *IId* being also formed. Exposure of the mixture of the positional isomers, *IVh*, to the action of sulphuric acid at room temperature gave rise to two derivatives of benzo(*c*)fluorene, *VIa* and *VIb*, where the ester function was demonstrated in position 6 of the aromatic skeleton. This corresponds, in view of the ring closure, to the reaction of that positional isomer in which the carboxylic group is fixed in position 3 of the naphthalene ring. The other isomer failed to be isolated from the reaction mixture, evidently owing to its destruction.



Va, $R^1 = H$
Vb, $R^1 = CH_3$
Vc, $R^1 = C_2H_5$



VIa, $R^1 = H$
VIb, $R^1 = CH_3$

In the pharmacological evaluation for antineoplastic efficacy in tumours transplanted on animals some of the compounds exhibited moderate antineoplastic effects, comparable with those of the starting dicyano derivatives. Derivatives of 7--oxo-7*H*-benzo(*c*)fluorene, *Va–c*, administered *s.c.* or *p.o.*, exhibited marked antiviral effects in animals infected with encephalomyocarditis virus or vaccinia virus. These compounds have also proved to be capable of generating interferon. A more detailed evaluation of the biological action of these compounds will be published elsewhere.

EXPERIMENTAL

The melting points of the compounds were determined on the Kofler block and are not corrected. Samples for elemental analysis were dried over phosphorus pentoxide at a pressure of 70 Pa and temperatures proportional to their melting points. Homogeneity of the samples and composition of the reaction mixtures were followed by TLC on reflex foils Silufol UV_{254} (Kavalier) and by the quenching of UV light at 254 nm, a Universal UV-Lampe Camag (Muttenz-Schweiz) being employed. The reaction mixtures were resolved by column chromatography on Kieselgel 60 reinst (Merck). ^{1}H-NMR spectra were measured in an apparatus Tesla BS487C (80 MHz), 10% solutions of the compounds and tetramethylsilane as internal standard being employed. IR spectra were measured with spectrometers Perkin–Elmer 577 and Infrascan Hilger. Mass spectra were recorded in an apparatus MS-9.

Procedures of Hydrolysis of Compounds *Ia—g*

Method A: A suspension of *Ia* or *Ic* (ref.[3]) in ethanol containing 10% of water and 10 mol equivalents of potassium hydroxide was refluxed for 3 h. After evaporation of the volatile components the residue was dissolved in water and the solution brought to pH 2 with dilute hydrochloric acid. The separated solid was collected on a filter, washed with water and dried. The product was dissolved in benzene. The solution was filtered and chromatographed on a column of silica gel (30-fold weight amount of the sample), containing, in its upper third, 5% of active carbon (to absorb the yellow dyes), benzene or a mixture of it and chloroform being used as eluant.

Method B: A mixture of *Ic* (10·2 g, 0·03 mol) and potassium hydroxide (16·8 g, 0·3 mol) in 180 ml of ethylene glycol was refluxed for 8 h, diluted with 200 ml of water and refluxed for another 3 h. After further dilution of the mixture with 800 ml of water and extraction with two 100 ml portions of chloroform the aqueous layer was brought to pH 2 with hydrochloric acid and the precipitate was taken into three 100 ml portions of chloroform. The combined chloroform extracts were dried with anhydrous magnesium sulphate and taken to dryness. Column chromatography on silica gel, with benzene containing 1% of ethanol as eluant, gave compound *IVa* (1·4 g, 14·6%) in the first fractions. The following fractions contained a mixture of compounds *IVb* and *IVc* (4·8 g), which was dissolved in 150 ml of chloroform and extracted with a 3%solution of sodium hydrogen carbonate (3 × 200 ml). The combined alkaline portions were brought to pH 2 with hydrochloric acid and the precipitate was taken into three 50 ml portions of chloroform, which were combined and concentrated to crystallize; yield 3·2 g (33·4%) of compound *IVb*. After separation of the latter further concentration of the chloroform solution gave crystals of compound *IVc* (1·1 g, 11·5%).

IVa: ^{1}H-NMR spectrum (hexadeuterodimethyl sulphoxide): δ 8·00 (bs, 1 H, $C_{(8)}$—H), 7·20 (m, 6 H, Ar—H), 6·90 (s, 1 H, $C_{(3)}$—H), 2·77 (q, 2 H, J = 7·0 Hz, Ar—CH_2), 2·66 (q, 2 H, J = = 7·0 Hz, Ar—CH_2), 1·27 (t, 6 H, J = 7·0 Hz, ArCH_2—CH_3). IR spectrum (KBr): 1 668 cm^{-1} (C=O···HO—).

IVb: ^{1}H-NMR spectrum (hexadeuterodimethyl sulphoxide): δ 8·02 (bs, 1 H, $C_{(8)}$—H), 7·30 (m, 2 H, $C_{(5)}$, $C_{(6)}$—H), 7·22 (s, 1 H, $C_{(3)}$—H), 7·25, 7·10 (ABq, 4 H, J = 8·5 Hz, *para*-substituted Ar), 2·77 (q, 2 H, J = 7·0 Hz, Ar—CH_2), 2·67 (q, 2 H, J = 7·0 Hz, Ar—CH_2), 1·26 (t, 6 H, J = 7·0 Hz, ArCH_2—CH_3). IR spectrum (KBr): 1 698 cm^{-1} (C=O acid).

IVc: ^{1}H-NMR spectrum (hexadeuterodimethyl sulphoxide): δ 8·00 (bs, 1 H, ($C_{(8)}$—H), 7·20 (m, 6 H, Ar—H), 6·94 (s, 1 H, $C_{(2)}$—H), 2·75 (q, 2 H, J = 7·0 Hz, Ar—CH_2), 2·65 (q, 2 H, J = 7·0 Hz, Ar—CH_2), 1·23 (t, 6 H. J = 7·0 Hz, ArCH_2—CH_3). IR spectrum (KBr): 1 658 cm^{-1} (C=O amide).

Method C: A suspension of compound *Ia—g* in a mixture of acetic acid, water and sulphuric acid was refluxed for 3—10 h, cooled and poured into water. The precipitate was collected on a filtre, washed with water and dried. The mixture of products was resolved by crystallization or column chromatography.

Hydrolysis of Compound *Ia*

Method A: Compound *Ia* (22·7 g, 0·08 mol), potassium hydroxide (44·8 g, 0·8 mol) and 250 ml of 90% ethanol. Yields: Compound *IIe*, 8·8 g (34·6%), and *IIIa*, 9·5 g (37·4%). *IIe*: IR spectrum ($CHCl_3$): 1 245, 1 260 (C—O anhydride), 1 530, 1 568, 1 600 (Ar), 1 768, 1 826 cm^{-1} (C=O anhydride). *IIIa*: ^{1}H-NMR spectrum (hexadeuterodimethyl sulphoxide): δ 11·40 (bs, 1 H, NH),

8·50 (m, 1 H, $C_{(8)}$—H), 7·20—7·90 (m, 8 H, Ar—H), 4·58 (q, 2 H, J = 7·0 Hz, O—CH_2), 1·48 (t, 3 H, J = 7·0 Hz, OCH_2—CH_3). IR spectrum (KBr): 1 510, 1 590 (Ar), 1 700, 1 756 cm^{-1} (—CO—NH—CO—).

Method C: *Ia* (20·0 g, 0·07 mol), 600 ml of acetic acid, 300 ml of water and 340 ml of sulphuric acid, reflux for 10 h. Column chromatography, benzene–tetrachloromethane (1 : 1) as eluant. Yields: *IIa*, 11·2 g (52·6%), and *Va*, 7·2 g (18·9%); a trace of *IVg* was also obtained. *IIa*: ^{1}H-NMR spectrum (hexadeuterodimethyl sulphoxide): δ 8·55 (m, 1 H, $C_{(8)}$—H), 7·20—8·00 (m, 8 H, Ar—H), 4·41 (s, 3 H, OCH_3). IR spectrum (KBr): 710 (monosubstituted Ar), 750 (*ortho*-disubstituted Ar), 1 525, 1 610 (Ar), 1 780, 1 830 (C=O anhydride), 1 225, 2 860 cm^{-1} (OCH_3). *IVg*: ^{1}H-NMR spectrum (hexadeuterodimethyl sulphoxide): δ 10·45 (bs, 1 H, phenol OH), 8·20 (m, 1 H, $C_{(8)}$—H), 7·40 (m, 8 H, Ar—H), 7·18 (bs, 2 H, $CONH_2$), 6·95 (s, 1 H, $C_{(2)}$—H). IR spectrum (KBr): 1 600 (Ar), 1 640 (C=O amide), 3 200 (OH-phenol), 3 320, 3 440 cm^{-1} (NH_2). Mass spectrum *m/e*: 263 (M^+ $C_{17}H_{10}NO_2$). *Va*: IR spectrum (KBr): 1 520, 1 580, 1 610 (Ar), 1 710 (C=O), 3 400 cm^{-1} (OH). Mass spectrum, *m/e*: 246 ($M^+C_{17}H_{10}O_2$).

Hydrolysis of Compound *Ib*

Method C: *Ib* (17·5 g, 0·056 mol), 490 ml of acetic acid, 280 ml of water, 420 ml of sulphuric acid, reflux for 3·5 h. The crude product was extracted with boiling benzene. The undissolved portion was crystallized; yield *Vb*, 4·6 g (30·0%). The benzene filtrate gave a crude portion of *IIb*, which was purified by column chromatography; yield 9·2 g (49·5%). *IIb* ^{1}H-NMR spectrum ($CDCl_3$): δ 8·32 (bs, 1 H, $C_{(8)}$—H), 7·73 (d, 1 H, J = 8·0 Hz, $C_{(5)}$—H), 7·50 (dd, 1 H, J = 2·0; 8·0 Hz, $C_{(6)}$—H), 7·38, 7·21 (ABq, 4 H, J = 8·5 Hz, para-substituted Ar), 4·49 (s, 3 H, OCH_3), 2·59 (s, 3 H, $ArCH_3$), 2·48 (s, 3 H, $ArCH_3$). Mass spectrum, *m/e*: 332 (M^+ $C_{21}H_{16}O_4$). *Vb*: ^{1}H-NMR spectrum (hexadeuterodimethyl sulphoxide): δ 10·70 (s, 1 H, OH), 8·25 (d, 1 H, J = = 8·0 Hz, $C_{(1)}$ or $C_{(11)}$—H), 8·00 (bs, 1 H, $C_{(4)}$—H), 7·78 (d, 1 H, J = 8·0 Hz, $C_{(1)}$ or $C_{(11)}$— —H), 7·42 (bs, 1 H, J = 8·0 Hz, $C_{(10)}$ or $C_{(12)}$—H, 7·25 (bs, 1 H, $C_{(8)}$—H), 7·21 (bd, 1 H, J = = 8·0 Hz, $C_{(10)}$ or $C_{(12)}$—H), 6·98 (s, 1 H, $C_{(6)}$—H), 2·50 (s, 3 H, Ar—CH_3), 2·29 (s, 3 H, Ar—CH_3).
IR spectrum (KBr): 1 580, 1 625 (Ar), 1 710 (C=O), 3 420 cm^{-1} (phenol OH). Mass spectrum. *m/e*: 274 (M^+ $C_{19}H_{14}O_2$).

Hydrolysis of Compound *Ic*

Method A: *Ic* (10·2 g, 0·03 mol) and potassium hydroxide (16·8 g, 0·3 mol) in 1 000 ml of 90% ethanol. Column chromatography gave successively: *IIc* (5·6 g, 49·8%), *IVf* (150 mg, 1·23%), *IIIb* (3·7 g, 33·0%) and *Ig* (650 mg, 6·6%. *IIc*: ^{1}H-NMR spectrum ($CDCl_3$): δ 8·32 (bs, 1 H, $C_{(8)}$—H), 7·73 (d, 1 H, J = 8·0 Hz, $C_{(5)}$—H), 7·50 (dd, 1 H, J = 2·0; 8·0 Hz, $C_{(6)}$—H), 7·38, 7·21 (ABq, 4 H, J = 8·5 Hz, *para*-substituted Ar), 4·78 (q, 2 H, J = 7·0 Hz, —OCH_2—), 2·90 (q, 2 H, J = 7·0 Hz, Ar—CH_2), 2·80 (q, 2 H, J = 7·0 Hz, Ar—CH_2), 1·60 (t, 3 H, J = 7·0 Hz, OCH_2— —CH_3), 1·37 (t, 6 H, J = 7·0 Hz, $ArCH_2$—CH_3). *IIIb*: ^{1}H-NMR spectrum ($CDCl_3$): δ 8·25 (bs, 2 H, $C_{(8)}$—H, NH), 7·65 (d, 1 H, J = 8·0 Hz, $C_{(5)}$—H), 7·40 (dd, 1 H, $C_{(6)}$—H), 7·32, 7·18 (ABq, 4 H, *para*-substituted Ar), 4·75 (q, 2 H, J = 7·0 Hz, O—CH_2), 2·85 (q, 2 H, J = 7·0 Hz, Ar—CH_2), 2·75 (q, 2 H, J = 7·0 Hz, Ar—CH_2), 1·55 (t, 3 H, J = 7·0 Hz, OCH_2—CH_3), 1·31 (t, 6 H, J = 7·0 Hz, $ArCH_2$—CH_3). IR spectrum ($CHCl_3$): 1 510, 1 590 (Ar), 1 720, 1 760 (CONHCO), 3 250 (NH ass.), 3 420 cm^{-1} (NH free). *IVf*: ^{1}H-NMR spectrum (hexadeuterodimethyl sulphoxide): δ 7·98 (bs, 1 H, $C_{(8)}$—H), 7·40 (m, 2 H, $C_{(5)}$, $C_{(6)}$—H), 4·20 (q, 2 H, J = = 7·0 Hz, OCH_2—), 3·85 (s, 3 H, $COOCH_3$), 2·80 (q, 2 H, J = 7·0 Hz, Ar—CH_2), 2·70 (q, 2 H, J = 7·0 Hz, Ar—CH_2), 1·48 (t, 3 H, J = 7·0 Hz, OCH_2CH_3), 1·28 (t, 6 H, J = 7·0 Hz, $ArCH_2$—

—CH_3). IR spectrum (KBr): 830 (*para*-substituted Ar), 1 190 (O—CH_3), 1 220 (O—C_2H_5), 1 570, 1 600 (Ar), 1 708 (C=O acid), 1 740 cm^{-1} (C=O ester).

Method C: *Ic* (19·8 g, 0·058 mol), 560 ml of acetic acid, 320 ml of water, 480 ml of sulphuric acid, reflux for 3 h. Column chromatography with tetrachloromethane as eluant gave *IId* (14·5 g, 69·3%) and, after elution with tetrachloromethane–chloroform (1 : 3), *Vc* (1·4 g, 8·1%). *IId*: IR spectrum (KBr): 760 (*ortho*-disubstituted Ar), 1 585, 1 610, 1 620 (Ar), 1 760, 1 820 (C=O anhydride), 1 225, 2 860 cm^{-1} (OCH_3). *Vc*: ^{1}H-NMR spectrum (hexadeuterodimethyl sulphoxide): δ 10·71 (s, 1 H, OH), 8·22 (d, 1 H, J = 8·0 Hz, $C_{(1)}$ of $C_{(11)}$—H), 7·98 (bs, 1 H, $C_{(4)}$—H), 7·74 (d, 1 H, J = 8·0 Hz, $C_{(1)}$ or $C_{(11)}$—H), 7·44 (bd, 1 H, J = 8·0 Hz, $C_{(10)}$ or $C_{(12)}$—H), 7·25 (bs, 1 H, $C_{(8)}$—H), 7·18 (bd, 1 H, J = 8·0 Hz, $C_{(10)}$ or $C_{(12)}$—H), 6·97 (s, 1 H, $C_{(6)}$—H), 2·76 (q, 2 H, J = 7·0 Hz, Ar—CH_2), 2·58 (q, 2 H, J = 7·0 Hz, Ar—CH_2), 1·28 (t, 3 H, J = = 7·0 Hz, Ar—CH_2—CH_3), 1·16 (t, 3 H, J = 7·0 Hz, ArCH_2—CH_3). IR spectrum (KBr): 1 582, 1 624 (Ar), 1 710 (C=O), 3 420 cm^{-1} (phenol OH).

Hydrolysis of Compound *Id*

Method C: *Id* (4·8 g, 0·013 mol), 140 ml of acetic acid, 80 ml of water, 120 ml of sulphuric acid, reflux 3 h; yield 3·4 g (86·5%) of *Vc*.

Hydrolysis of Compound *Ie*

Method C: *Ie* (28·1 g, 0·103 mol), 700 ml of acetic acid, 400 ml of water, 595 ml of sulphuric acid, reflux for 6 h. The crude product was washed 10 min in 1 l of boiling water, filtered and dried; yield 23·1 g (91%) of *Va*.

Hydrolysis of Compound *If*

Method C: *If* (0·289 g, 0·001 mol) 6·8 ml of acetic acid, 3·8 ml of water, 5·7 ml of sulphuric acid, reflux for 6·5 h. The crude product was washed 10 min in 10 ml of boiling water. Crystallization gave 0·186 g (67·8%) of *Vb*.

Hydrolysis of Compound *Ig*

Method C: *Ig* (0·98 g, 0·003 mol), 20 ml of acetic acid, 10 ml of water, 20 ml of sulphuric acid, reflux for 3 h. The crude product was purified by crystallization; yield 0·5 g (55·2%) of *Vc*.

Ring Closure of Compound *IIc*

A solution of *IIc* (0·374 g, 0·001 mol) in a mixture of 6·7 ml of acetic acid, 3·8 ml of water and 5·7 ml of sulphuric acid was refluxed for 8 h and poured into water. The precipitate was collected on a filter, washed with water and dried. Crystallization gave 0·2 g (66·3%) of *Vc*.

Esterification of Compound *IVb*

A suspension of *IVb* (4·2 g, 0·013 mol) in a mixture of 50 ml of tetrachloromethane, 5 ml of methanol and 0·5 ml of sulphuric acid was refluxed for 12 h. Following extraction with three 30 ml portions of a 2% aqueous solution of sodium hydrogen carbonate and 20 ml of water, the organic layer was concentrated to crystallize; yield 2·5 g (57·4%) of *IVd* ^{1}H-NMR spectrum ($CDCl_3$): δ 8·08 (bs, 1 H, $C_{(8)}$—H), 7·50 (d, 1 H, J = 8·0 Hz, $C_{(5)}$—H), 7·31 (d, 1 H, J = 2·0; 8·0 Hz,

$C_{(6)}$—H), 7·20, 7·10 (ABq, 4 H, J = 8·5 Hz, *para*-substituted Ar), 7·20 (s, 1 H, $C_{(2)}$—H), 3·52 (s, 3 H, $COOCH_3$), 2·80 (q, 2 H, J = 7·0 Hz, Ar—CH_2), 2·70 (q, 2 H, J = 7·0 Hz, Ar—CH_2), 1·25 (t, 3 H, J = 7·0 Hz, $ArCH_2$—CH_3).

Methanolysis of Compound *IId*

A solution of *IId* (8·0 g, 0·022 mol) in a mixture of 50 ml of chloroform and 100 ml of methanol was refluxed for 16 h. After evaporation of the volatile components the crude product was purified by column chromatography (10-fold amount of silica gel, benzene with 1% of ethanol as eluant). The unreacted compound was removed from the first fractions and 6·7 g (77·7)% of *IVh* was obtained. ^{1}H-NMR spectrum ($CDCl_3$): δ 10·35 (bs, 1 H, COOH), 8·00 (bs, 1 H, $C_{(8)}$—H), 7·52 (d, 1 H, J = 8·0 Hz, $C_{(5)}$—H), 7·30 (dd, 1 H, J = 2·0; 8·0 Hz, $C_{(6)}$—H), 7·29, 7·20 (ABq, 4 H, J = 8·5 Hz, *para*-substituted Ar), 4·12, 4·10 (s, Σ 3 H, $ArOCH_3$), 3·90 (s, 1·5 H, $C_{(2)}$—$COOCH_3$), 3·52 (s, 1·5 H, $C_{(3)}$—$COOCH_3$), 2·82 (q, 2 H, J = 7·0 Hz, Ar—CH_2), 2·72 (q, 2 H, J = 7·0 Hz, Ar—CH_2), 1·30 (t, 6 H, J = 7·0 Hz, $ArCH_2$—CH_3).

Esterification of Compound *IVh*

A solution of *IVh* (3·92 g, 0·001 mol) in a mixture of dichloroethane (20 ml), methanol (2 ml) and sulphuric acid (0·3 ml) was refluxed for 16 h, concentrated, dissolved in 100 ml of chloroform, extracted with three 50 ml portions of a 2% aqueous solution of sodium hydrogen carbonate and once with water. The chloroform layer was dried with anhydrous magnesium sulphate and concentrated to crystallize; yield 1·0 g (27·7%) of *IId*. Column chromatography of the mother liquor freed from *IId*, with benzene as eluant, gave *IVe*, 2·0 g (49·3%). ^{1}H-NMR spectrum ($CDCl_3$) δ 8·00 (bs, 1 H, $C_{(8)}$—H), 7·53 (dd, 1 H, J = 8·0 Hz, $C_{(5)}$—H), 7·30 (dd, 1 H, J = 2·0; 8·0 Hz, $C_{(6)}$—H), 7·28, 7·18 (ABq, 4 H, J = 8·5 Hz, *para*-substituted Ar), 4·10 (s, 3 H, ArCO—CH_3), 3·90 (s, 3 H, $C_{(2)}$—$COOCH_3$), 3·50 (s, 3 H, $C_{(3)}$—$COOCH_3$), 2·82 (q, 2 H, J = 7·0 Hz, Ar—CH_2), 2·72 (q, 2 H, J = 7·0 Hz, Ar—CH_2), 1·30 (t, 3 H, $ArCH_2$—CH_3).

Reaction of Compound *IVh* with Sulphuric Acid

A solution of *IVh* (0·785 g, 0·002 mol) in 8 ml of sulphuric acid was stirred for 8 h at 20—25°C, then poured on 50 g of crushed ice. The precipitate was taken into chloroform (3 × 10 ml). The chloroform solution was extracted with 20 ml of water, dried with anhydrous magnesium sulphate, concentrated and resolved by column chromatography on silica gel, with benzene as eluant. The qualitatively identical fractions were combined, concentrated and allowed to crystallize. Yields: *VIa* (130 mg, 18%) and *VIb* (80 mg, 10·7%). *VIa*: ^{1}H-NMR spectrum ($CDCl_3$): δ 11·39 (s, 1 H, OH), 8·25 (d, 1 H, J = 8·0, $C_{(1)}$ or $C_{(11)}$—H), 8·18 (d, 1 H, J = 1·5 Hz, $C_{(4)}$—H), 7·65 (d, 1 H, J = 8·0 Hz, $C_{(1)}$ or $C_{(11)}$—H), 7·50 (dd, 1 H, J = 1·5; 8·0 Hz, $C_{(2)}$ or $C_{(10)}$—H), 7·36 (d, 1 H, J = 1·5 Hz, $C_{(8)}$—H), 7·18 (dd, 1 H, J = 1·5; 8·0 Hz, $C_{(2)}$ or $C_{(10)}$—H), 4·00 (s, 3 H, $COOCH_3$), 2·80 (q, 2 H, J = 7·0 Hz, Ar—CH_2), 2·60 (q, 2 H, J = 7·0 Hz, Ar—CH_2), 1·31 (t, 3 H, $ArCH_2$—CH_3), 1·21 (t, 3 H, $ArCH_2$—CH_3). IR spectrum ($CHCl_3$): 1 580, 1 620 (Ar), 1 670 (C=O···HO ester), 1 710 (C=O ketone), 2 870 (OCH_3), 3 150 cm^{-1} (OH). *VIb*: ^{1}H-NMR spectrum ($CDCl_3$): δ 8·25 (d, 1 H, J = 8·0 Hz, $C_{(1)}$ or $C_{(11)}$—H), 7·88 (d, 1 H, J = 1·5 Hz, $C_{(4)}$—H), 7·69 (d, 1 H, J = 8·0 Hz, $C_{(1)}$ or $C_{(11)}$—H), 7·40 (dd, 1 H, J = 1·5; 8·0 Hz, $C_{(2)}$ or $C_{(10)}$—H), 7·35 (d, 1 H, J = 1·5 Hz, $C_{(8)}$—H), 7·20 (dd, 1 H, J = 1·5; 8·0 Hz, $C_{(2)}$ or $C_{(10)}$—H), 4·05 (s, 3 H, $ArOCH_3$), 4·00 (s, 3 H, $COOCH_3$), 2·80 (q, 2 H, J = 7·0 Hz, Ar—CH_2), 2·60 (q, 2 H, J = 7·0 Hz, Ar—CH_2), 1·31 (t, 3 H, J = 7·0 Hz, $ArCH_2$—CH_3), 1·21 (t, 3 H, J = 7·0 Hz, $ArCH_2$—CH_3). IR spectrum ($CHCl_3$): 1 580, 1 600, 1 625 (Ar), 1 710 (C=O ketone), 1 740 (C=O ester), 2 870 cm^{-1} (OCH_3).

The elemental analyses were performed by Mrs J. Komancová and Mrs J. Kropáčová in the Analytical Department of the Institute (head: Dr J. Körbl). Antineoplastic efficacy was evaluated by Mrs. S. Pokorná in the Pharmacological Department of the Institute (head: Dr K. Řežábek). The preliminary antiviral screening was carried out by Dr F. Šmejkal and coworkers in the Virological Department of the Institute (head: Dr F. Šmejkal).

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