THE SYNTHESIS OF MODEL LACTONES OF CYCLOLIGNAN TYPE*

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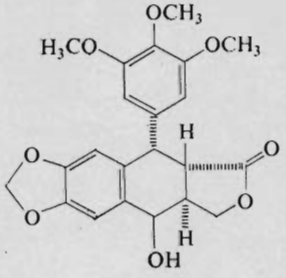
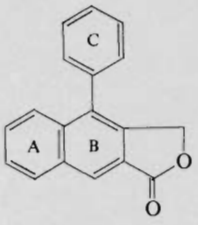
Lactones *VI*—*IX* were prepared on reduction of anhydrides of 4-aryl-1-methoxynaphthalene-2,3-dicarboxylic acids *IV* and *V* with sodium borohydride in methanol. Catalytic hydrogenation on platinum of lactones *VIII* and *IX* gave lactones with hydrogenated ring A, or A and C. Lactones *XII* and *XIII* were found to possess an inhibitory effect on the growth of the tumour S 37 in experimental animals.

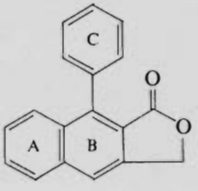
Podophylotoxin (*I*) and related cyclolignan lactones assume an important place among chemotherapeutic agents against tumours[1,3]. Much effort has been spent on the total synthesis of compounds of this type[4-8]. Natural cyclolignan lactones occur either as 4-aryl or as 9-arylnaphtho[2,3-*c*]-furan-1(3*H*)-ones (*II*, *III*), while the B rings may be aromatic or heteroaromatic.



I



II



III

In previous communications we described the synthesis of derivatives of 4-aryl-1-naphthol substituted in positions 2 and 3 of the B ring with various substituents[9-12]. In view of the structural resemblance of these substances to cyclolignans we tried to functionalize the B ring with a lactone function, using anhydrides of 4-aryl-1-methoxynaphthalene-2,3-dicarboxylic acids[12] (*IV*, *V*) as starting compounds. In this communication we described the course of reduction of anhydrides *IV* and *V*

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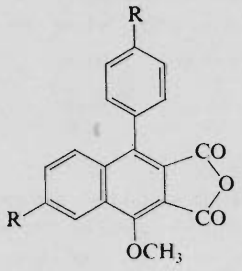
to corresponding lactones *VI*–*IX* and the products of reduction of the aromatic skeleton of selected lactones *VIII* and *IX* (Table I).

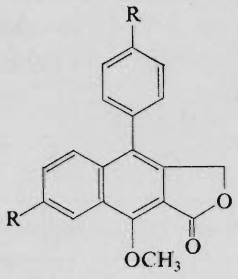
Anhydrides *IV* and *V* may be reduced analogously as in literature for example with zinc in acetic acid[13,14] or with lithium aluminum hydride at low temperatures[14]. In both cases mixtures of lactones are formed and when hydride is used hydroxy derivatives are also present in the reaction mixture. In our experiments we reduced anhydrides *IV* and *V* with sodium borohydride in methanol. From the reaction mixtures lactone *VI* or *VIII* were isolated, respectively, in an approximately 2 : 1 ratio with respect to lactone *VII* or *IX*. This fact indicates an easier reducibility of the oxo group sterically hindered by the neighbouring substituent, in agreement with the literature data[14,15]. Further we tried to reduce anhydride *V* with sodium acetyloxyborohydride prepared *in situ*[16]. We obtained the same ratio of lactones *VIII* and *IX* as when sodium borohydride was used. In both cases it was indispensable to use an excess of the reducing agents.

TABLE I
Some Lactones of Cyclolignan Type

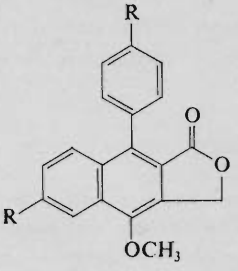
Compound	Formula (mol.weight)	M.p., °C (solvent)	Yield %	Calculated/Found	
				% C	% H
VI	$C_{19}H_{14}O_3$ (290·3)	113–115 (methanol)	43·9	78·61 78·88	4·86 4·85
VII	$C_{19}H_{14}O_3$ (290·3)	194–196 (methanol)	20·8	78·61 78·15	4·86 4·70
VIII	$C_{23}H_{22}O_3$ (346·4)	93–94 (chloroform) methanol)	60·8	79·74 79·98	6·40 6·49
IX	$C_{23}H_{22}O_3$ (346·4)	101–103 (methanol)	28·2	79·74 79·79	6·40 6·26
X	$C_{23}H_{26}O_3$ (350·5)	118–120 (hexane)	9·8	78·82 78·86	7·48 7·57
XI	$C_{23}H_{32}O_3$ (356·5)	124–126 (hexane)	53·0	77·49 77·62	9·05 9·12
XII	$C_{23}H_{26}O_3$ (350·5)	97–99 (hexane)	15·4	78·82 78·95	7·48 7·70
XIII	$C_{23}H_{32}O_3$ (356·5)	105–107 (hexane)	58·8	77·49 77·53	9·05 9·26



IV, R = H
V, R = C_2H_5

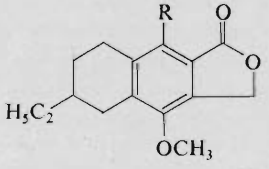


VI, R = H
VIII, R = C_2H_5

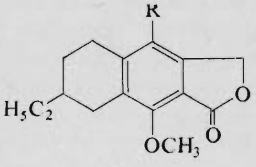


VII, R = H
IX, R = C_2H_5

Lactones *VIII* and *IX* were hydrogenated in acid medium on Adams catalyst at elevated temperature and pressure. From the reaction mixture we isolated both the products with hydrogenated A ring (lactones *X*, *XII*) and the products with hydrogenated A and C rings (lactones *XI*, *XIII*) (see Table I). The B ring, carrying the lactone grouping remained aromatic in agreement with the results of reduction of analogous compounds[14].



X, R = 4-C_2H_5—C_6H_4
XI, R = 4-C_2H_5—C_6H_{10}-cyclo



XII, R = 4-C_2H_5—C_6H_4
XIII, R = 4-C_2H_5—C_6H_{10}-cyclo

The structure of selected compounds was proved by IR and ^{1}H-NMR spectroscopy. The characteristic vibrations at 1760–1770 cm^{-1} in the IR spectrum correspond to the lactone grouping. In the ^{1}H-NMR spectrum of lactones *VI* and *VIII* the hydrogens of the methylene group of the lactone are shielded by the neighbouring aromatic nucleus and their peaks undergo – in comparison with lactones *IX* and *XII* – a shift to lower δ-value by 0·4 ppm. In contrast to this the hydrogens of the methoxyl group on carbon $C_{(1)}$ are shifted in lactones *VI* and *VIII* by about 0·3 to 0·4 ppm to higher δ-values in consequence of the effect of the shielding by the carbonyl group in the *ortho* position.

Some of the synthetized compounds were evaluated for their antineoplastic activity in animals with experimental transplantable tumours S 180 and S 37, using a 100 mg/kg dose applied per os for 8 days. Lactones *VI*–*IX* were inactive in these

tests, while lactones *XII* and *XIII* showed a statistically significant effect on the diminution of the size of the tumour S 37, in the range of 20–25%, while the time of survival of the animals was not affected when compared with the controls.

EXPERIMENTAL

The melting points of the compounds were determined on a Kofler block and they are not corrected. Samples for elemental analysis were dried at temperatures proportional to melting points, over phosphorus pentoxide and *in vacuo*, 70 Pa. The homogeneity of the samples and of the reaction mixtures was checked by TLC on reflexing foils Silufol UV_{254} (Kavalier), observing the quenching of fluorescence at 254 nm produced with a Universal UV-Lamp Camag (Muttenz, Switzerland). The separation of the reaction mixtures was carried out by column chromatography on Kieselgel 60 reinst (Merck), generally on a 30 fold amount of the sample weight. The ^{1}H-NMR spectra were measured on a Tesla BS487C (80 MHz) instrument, using 10% solutions in deuteriochloroform and TMS as internal reference. The IR spectra were measured on a Perkin–Elmer 577 instrument, using 5% solutions in chloroform or the KBr pellets technique.

Reduction of Anhydrides of 4-Aryl-1-methoxynaphthalene-2,3-dicarboxylic Acids (*IV*, *V*) to Lactones *VI*–*IX*

Sodium borohydride (a total of 12 g; 0·3 mol) was added in 10 portions over one hour and at 40°C to a solution of 6·08 g (20 mmol) of anhydride *IV*, or 7·2 g (20 mmol) of anhydride *V*, in 600 ml of methanol. When the development of hydrogen ceased the mixture was refluxed for 2 h. After evaporation of methanol in a vacuum the residue was dissolved in 600 ml of water, acidified with dilute hydrochloric acid (1 : 1) to pH 3 and the separated precipitate was extracted with chloroform (3 × 100 ml). The chloroform fractions were combined and extracted with an equal amount of water, then dried over anhydrous sodium sulfate and evaporated. The crude mixture of lactones *VI* and *VII* (from *IV*) or *VIII* and *IX* (from *V*) was separated by column chromatography using tetrachloromethane–5% benzene (*VI* and *VII*) or benzene–cyclohexane (1 : 1) (*VIII* and *IX*), respectively. First lactones *VI* or *VIII* were eluted and in latter fractions lactones *VII* or *IX*. Chromatographically pure fractions were combined and purified by crystallization (Table I).

VI: ^{1}H-NMR spectrum: δ 8·50 (m, 1 H, 8 H), 7·10–7·90 (m, 8 H, Ar—H,) 5·15 (s, 2 H, Ar—CH_2—O), 4·40 (s, 3 H, OCH_3). IR spectrum: 1 758 (C=O lactone), 1 620, 1 600, 1 590 cm^{-1} (Ar).

VII: IR spectrum: 1 762 (C=O lactone), 1 620, 1 600, 1 588, 1 570 cm^{-1} (Ar).

VIII: ^{1}H-NMR spectrum: δ 8·25 (mcs, 1 H, J = 1·5 Hz, 8-H), 7·68 (d, 1 H, J = 8·0 Hz, 5-H), 7·40 (mcd, 1 H, J = 8·0; 1·5 Hz, 6-H), 7·38, 7·20 (ABq, 4 H, J = 8·5 Hz, *p*-substituted Ar), 5·15 (s, 2 H, Ar—CH_2—O), 4·40 (s, 3 H, OCH_3), 2·83 (q, 2 H, J = 7·0 Hz, Ar—CH_2—), 2·78 (q, 2 H, J = 7·0 Hz, Ar—CH_2—), 1·35 (t, 6 H, J = 7·0 Hz, Ar—CH_2—CH_3). IR spectrum (KBr): 1 752 (C=O lactone), 1 616, 1 608, 1 585 cm^{-1} (Ar).

IX: ^{1}H-NMR spectrum: δ 8·10 (mcs, 1 H, J = 1·5 Hz, 8-H), 7·70 (d, 1 H, J = 8·0 Hz, 5-H), 7·35 (mcd, 1 H, J = 8·0; 1·5 Hz, 6-H), 7·35, 7·18 (ABq, 4 H, J = 8·5 Hz, *p*-substituted Ar), 5·55 (s, 2 H, Ar—CH_2—O), 4·12 (s, 3 H, OCH_3), 2·83 (q, 2 H, J = 7·0 Hz, Ar—CH_2—), 2·78 (q, 2 H, J = 7·0 Hz, Ar—CH_2—), 1·35 (t, 6 H, J = 7·0 Hz, Ar—CH_2—CH_3). IR spectrum (KBr): 1 765 (C=O lactone), 1 623, 1 610, 1 582, 1 520 cm^{-1} (Ar).

Catalytic Hydrogenation of Lactone *VIII* and *IX* to Lactone *X*—*XIII*

A solution of 1·04 g (3 mmol) of lactone *VIII* or *IX* in 50 ml of ethanol containing 1·0 g of dissolved hydrogen bromide and suspended 0·1 g of platinum oxide was hydrogenated in an autoclave at an initial hydrogen pressure of 10·1 MPa and at 100°C for 4 h. The catalyst was filtered off and the filtrate concentrated. The crude product, containing a mixture of lactones *X* and *XI*, or *XII* and *XIII*, respectively, was separated by column chromatography using a benzene–10% cyclohexane mixture. Lactone *XI*, or *XIII*, respectively, was separated in the first fractions, and it was followed by mixture of lactones *X* and *XI*, or *XII* and *XIII*, resp., in which lactone *X* or *XII*., resp., predominated. These mixtures were rechromatographed using benzene with 20% cyclohexane and pure fractions were obtained, containing lactone *X* or *XII*, respectively. Individual lactones were purified by crystallization.

XII: ^{1}H-NMR spectrum: δ 7·25, 7·03 (ABq, 4 H, J = 8·5 Hz, *p*-substituted Ar), 5·31 (s, 2 H, Ar—CH_2—O), 3·89 (s, 3 H, OCH_3), 2·69 (q, 2 H, J = 7·0 Hz, Ar—CH_2—), 1·29 (t, 3 H, J = = 7·0 Hz, Ar—CH_2—CH_3), 0·98 (bt, 3 H, $CHCH_2$—CH_3). IR spectrum: 1 770 (C=O lactone), 1 592 (Ar), 863 cm^{-1} (1,4-disubstituted aromatic ring). Mass spectrum: *m/e* 350·189 (M^+, corresponds to $C_{23}H_{26}O_2$).

XIII: ^{1}H-NMR spectrum: δ 5·25 (s, 2 H, Ar—CH_2—O), 3·80 (s, 3 H, OCH_3), 1·0 (bt, 6 H, $CHCH_2$—CH_3), IR spectrum: 1 760 (C=O lactone), 1 610, 1 592 cm^{-1} (Ar). Mass spectrum: *m/e* 356·236 (corresponds to $C_{23}H_{32}O_3$).

Reduction of Anhydride *V* with Sodium Acetyloxyborohydride

A solution of acetic acid (0·6 g; 10 mmol) in dioxane (5 ml) was added dropwise to a mixture of anhydride *V* (360 mg; 1 mmol) and sodium borohydride (380 mg; 10 mmol) in 10 ml of dioxane and the mixture was allowed to stand at about 15°C for 6 h. After decomposition of the reagent with 20 ml of water and acidification with hydrochloric acid to pH 3 the organic material was extracted with two 20 ml portions of chloroform. The combined extracts were dried over sodium sulfate and concentrated and the crude product was separated by column chromatography as in the experiment with sodium borohydride.

The analyses of the compounds described in this paper were carried out by Mrs J. Komancová of the analytical laboratory of our Institute (under the direction of Dr J. Körbl). The evaluation of the antineoplastic activity of the substances was carried out by Mrs S. Pokorná of the pharmacological department of our Institute (head of the department: Dr K. Řežábek).

REFERENCES

1. Kupchan S. M., Hemingway J. C., Knox J. R.: J. Pharm. Sci. *54*, 659 (1965).
2. Dombernowsky P., Nissen N. I., Larsen V.: Cancer Chemotherapy Rep. *56*, 71 (1972).
3. Dombernowsky P., Nissen N. I., Larsen V.: Brit. Med. J. *2*, 747 (1972).
4. Gensler W. J., Samour C. M., Wang S. Y., Johnson F.: J. Amer. Chem. Soc. *82*, 1714 (1960).
5. Gensler W. J., Gatsonis C. D.: J. Org. Chem. *31*, 4004 (1966).
6. Kende A. S., Liebeskond L. S., Mills J. E., Rutledge P. S., Curran D. P.: J. Amer. Chem. Soc. *99*, 7082 (1977).
7. Brown E., Robin J. P., Dhal R.: J. Chem. Soc. Chem. Commun. *1978*, 556.
8. Murphy W. S., Wattanasin S.: J. Chem. Soc. Chem. Commun. *1980*, 262.
9. Křepelka J., Holubek J., Semonský M.: This Journal *45*, 2695 (1980).

10. Křepelka J., Zikán V., Holubek J., Semonský M.: This Journal *45*, 2700 (1980).
11. Křepelka J., Vančurová I., Roubík J.: Czech. Appl. PV-7114-79.
12. Křepelka J., Semonský M.: Czech. No 195 766.
13. Bucher J. E.: J. Amer. Chem. Soc. *30*, 1244 (1908).
14. Ahmed R., Holmes T. L., Stevenson R.: J. Heterocycl. Chem. *11*, 687 (1974).
15. Bloomfield J. J., Lee S. L.: J. Org. Chem. *32*, 3919 (1967).
16. Umino N., Iwakuma T., Itoh N.: Tetrahedron Lett. *1976*, 763.

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