REACTIONS OF 4-ARYL-1-METHOXYNAPHTHALENE-2,3-DICARBOXYLIC ACID ANHYDRIDES AND NAPHTHO(2,3-*c*)FURAN-1-(3*H*)-ONE DERIVATIVES WITH HYDRAZINES*

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Reactions of anhydrides of 4-aryl-1-methoxynaphthalene-2,3-dicarboxylic acids, *Ia* and *Ib*, with hydrazine hydrate gave derivatives of benzo(*g*)phthalazine, *IV*–*VI*. Analogous reactions of the compounds *Ia* and *Ib* with hydrazines *IIIa* and *IIIb* afforded the corresponding N-aminoimides, *VII*–*X*. Derivatives of naphtho(2,3-*c*)furan-1(3*H*)-one, *IIa*–*IIc*, reacted with hydrazine hydrate with the formation of benzo(*f*)isoindoline-1(3*H*)-one derivatives, *XI*–*XIII*. In the antineoplastic screening the tested compounds have not proved efficacious.

The preceding communication of this series describes reactions of anhydrides of 4-aryl-1-alkoxynaphthalene-2,3-dicarboxylic acids with primary amines, giving rise to N-substituted cyclic imides[1]. As part of our studies we have now investigated the reactions of anhydrides of 4-aryl-1-methoxynaphthalene-2,3-dicarboxylic acids, *Ia* and *Ib* (ref.[2]), and of naphtho(2,3-*c*)-furan-1(3*H*)-one derivatives, *IIa*–*IId* (ref.[3]), with hydrazine and its derivatives *IIIa* and *IIIb*. We were interested in both the structures of the products, *IV*–*XIII*, and in their biological activity (Table I).

Analogous reactions of compounds having a cyclic anhydride grouping with hydrazine hydrate and some of its derivatives have been described[4,5]. These led, depending on the reaction conditions, to 1,2,3,4-tetrahydrobenzo(*g*)phthalazine compounds or to N-substituted imides of naphthalene-2,3-dicarboxylic acids, *i.e.* derivatives of benzo(*f*)isoindoline-1,3-dione. The formation of the six-membered or the five-membered rings was controlled by steric factors rather than by the nucleophilic character of the N^{α} atom in a hydrazine derivative[5].

Reaction of compound *Ia* with an excess of hydrazine hydrate in a boiling mixture gave a derivative of 4-hydrazino-1,2-dihydrobenzo(*g*)phthalazine, *IV*, as the only product, whereas an analogous reaction of compound *Ib* gave compounds *V* and *VI*, the latter probably being an intermediate. Reactions of compounds *Ia* and/or *Ib* with *IIIa* and/or *IIIb* led to substituted N-aminoimides of naphthalene-2,3-dicarbo-

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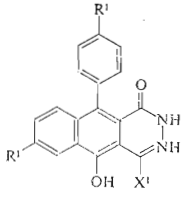
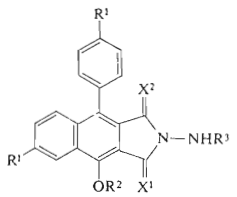
TABLE I
Reaction products



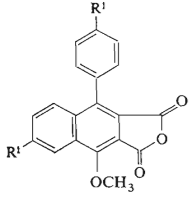
IV, V, VI



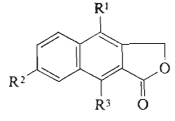
VII—XIII

Compound R^1	R^2 R^3	X^1 X^2	Formula (mol.mass)	M.p., °C (solvent)	Calculated/Found % C	% H	% N
IV	—	$NHNH_2$	$C_{18}H_{14}N_4O_2$	243—245	67·91	4·43	17·60
H	—	—	(318·3)	(ethanol)	68·21	4·76	17·86
V	—	$NHNH_2$	$C_{22}H_{22}N_4O_2$	272—275	70·57	5·92	14·96
C_2H_5	—	—	(374·5)	(methanol)	70·81	5·98	14·91
VI	—	OH	$C_{22}H_{20}N_2O_3$	278—280	73·31	5·59	7·77
C_2H_5	—	—	(360·4)	(benzene–methanol)	73·20	5·70	7·85
VII	H	O	$C_{24}H_{16}N_2O_3$	241—243	75·72	4·24	7·36
H	C_6H_5	O	(380·4)	(ethanol)	75·89	4·38	7·52
VIII	H	O	$C_{28}H_{24}N_2O_3$	104—107	77·04	5·54	6·41
C_2H_5	C_6H_5	O	(436·5)	(methanol)	77·48	5·72	6·65
IX	CH_3	O	$C_{29}H_{26}N_2O_3$	181—184	77·31	5·81	6·21
C_2H_5	C_6H_5	O	(450·6)	(methanol)	77·47	6·10	6·08
X	CH_3	O	$C_{29}H_{24}N_4O_7$	174—176	64·43	4·47	10·37
C_2H_5	$2,4\text{-}(NO_2)_2C_6H_3$	O	(540·5)	(methanol)	64·54	4·54	10·30
XI	H	O	$C_{18}H_{14}N_2O_2$	261—263	74·46	4·86	9·65
H	H	H_2	(290·3)	(benzene–ethanol)	74·51	5·01	9·34
XII	H	H^2	$C_{18}H_{14}N_2O_3$	306—308	74·46	4·86	9·65
H	H	O	(290·3)	(dimethyl-formamide)	74·56	5·10	9·60
XIII	H	H_2	$C_{22}H_{22}N_2O_2$	296—300	76·27	6·41	8·09
C_2H_5	H	O	(246·4)	(ethanol)	76·23	6·55	8·12

xylic acids, *VII–X* (Table I); the compound *IIIa* was used as the reaction medium and *IIIb* in a small excess in toluene. Formation of compounds *VII* and *VIII* was accompanied by demethylation of the starting compound. If the reaction was conducted under milder conditions in toluene (compound *X*) the demethylation did not occur. The formation of the derivatives of benzo(*f*)isoindoline-1(3*H*)-one, *XI–XIII*, was observed in the reactions of compounds *IIa–IIc* with an excess of hydrazine



Ia: $R^1 = H$
Ib: $R^1 = C_2H_5$



IIa: $R^1 = C_6H_5$, $R^2 = H$, $R^3 = OCH_3$
IIb: $R^1 = OCH_3$, $R^2 = H$, $R^3 = C_6H_5$
IIc: $R^1 = OCH_3$, $R^2 = C_2H_5$, $R^3 = 4\text{-}C_2H_5—C_6H_4$
IId: $R^1 = 4\text{-}C_2H_5—C_6H_4$, $R^2 = C_2H_5$, $R^3 = OCH_3$

$R^1—NH—NH_2$

IIIa: $R^1 = C_6H_5$
IIIb: $R^1 = 2,4\text{-}(NO_2)_2C_6H_3$

hydrate in boiling mixtures. Like in the above-mentioned reactions, the formation of compounds *XI–XIII* was accompanied by demethylation of the aromatic ether of the starting compound. Reaction of compound *IId* with hydrazine hydrate took a different course, probably leading to scission of the lactone cycle in compound *IIc*, whose structure we were not able to determine unequivocally.

The structures of the compounds were confirmed by IR, ^1H NMR and mass spectra. Convincing discrimination between the reaction courses of compounds *Ia*, *Ib* to products *IV–VI* and/or *VII–X* is based on the IR spectra. The double vibration of a carbonyl group at *c.* 1 700–1 730 cm^{-1} and at 1 750–1 770 cm^{-1} is characteristic of the cyclic imides *VII–X* (refs[1,6]). In the formation of the cyclic hydrazide structures *IV–VI* the IR spectra contain only one strong band at *c.* 1 640–1 660 cm^{-1} associated with the carbonyl group[7]. The reactions of the compounds *Ia*, *Ib* with hydrazine hydrate produced compounds *IV* and *V*, probably *via* the corresponding benzo(*g*)phthalazine-1,4-dione or its tautomeric forms, whose one oxo group under-

goes a consecutive reaction with hydrazine hydrate. The spectra did not allow us to decide safely on which oxo group the substitution had occurred. In view of the lesser steric hindrance at position 4 we suppose formation of 4-hydrazino derivatives to be a more probable one. The derivatives of benzo(*f*)isoindoline-1(3*H*)-one, *XI*–*XIII*, are characterised in their IR spectra by one vibration band of the amide carbonyl group at 1 635–1 650 cm^{-1}.

In assessing the biological efficacy *in vivo*, selected compounds were administered *p.o.* or *s.c.*, according to the usual screening scheme, to animals with experimental tumours. These were: S 180 (the Crocker sarcoma), Kr 2 (the Krebs ascitic tumour), HK (mammary gland adenocarcinoma), S 37 (ascitic sarcoma) and Y (the Yoshida ascitic tumour). In these tests the compounds failed to exhibit a substantial antitumourous effect; They either reduced the size of some of these tumours or extended survival of the animals by 20 to 40%. On a statistically significant scale, compound *IV* in a daily dose of 200 mg/kg *p.o.* extended survival of the animals with tumours S 180 by 23% and reduced the size of tumours S 37 by about 20%; compound *X* administered *p.o.* in the same dosage reduced the size of HK tumours by 27% and prolonged survival of the animals with Y tumours by 32%.

EXPERIMENTAL

The melting points of the compounds, determined on the Kofler block, are not corrected. Samples for elemental analyses were dried at temperatures adequate to their melting points at a pressure of 70 Pa over phosphorus pentoxide. Homogeneity of the samples and composition of the reaction mixtures were followed by TLC on reflex foils Silufol UV_{254} (Kavalier) by means of the quenching of UV light at 254 nm. The reaction mixtures were chromatographed on columns of Kieselgel 60 reinst (Merck). ^{1}H NMR spectra were measured with an apparatus Tesla BS497C (80 MHz); 10% solutions in deuteriochloroform or hexadeuterodimethyl sulphoxide and tetramethylsilane as internal standard were used. IR spectra were recorded with apparatuses Perkin–Elmer 577 and Infrascan Hilger; the KBr technique or 5% solutions in chloroform were used. Mass spectra were measured with an apparatus MS-9. Hydrazine hydrate was used as an 85% solution, unless otherwise specified.

Condensation of Anhydrides *Ia*, *Ib* and of Lactones *IIa*–*IIc* with Hydrazine Derivatives (Compounds *IV*–*XIII*)

Compounds *Ia,b* or *IIa*–*IId* were mixed with an excess of hydrazine hydrate or its derivative *IIIa*, or with 1·1 mol equivalents of *IIIb*, in toluene and the mixtures were refluxed for 3–16 h under nitrogen. They were then worked up as follows: *A*) after dilution with 10 volumes of water the precipitate was collected on a filter, washed with water and dried; *B*) after dilution with 10 volumes of water the precipitate was taken into three 500 ml portions of chloroform. These were combined, washed with the same volume of water and taken to dryness; *C*) the volatile components were distilled off *in vacuo*, the residue was stirred up in water and brought to pH 5 with concentrated hydrochloric acid. The precipitate was taken into chloroform. The crude products obtained by the three procedures were purified by crystallization or column chromatography.

IV: *Ia* (0·61 g, 0·002 mol), 4 ml of hydrazine hydrate, reflux for 3 h, procedure *A*. Crystallization gave 0·33 g (51·9%). IR spectrum (KBr): 1 540 (NH, amide), 1 598 (Ar), 1 640 (CO, amide), 3 240 cm^{-1} (NH, OH). ^1H NMR spectrum (hexadeuterodimethyl sulphoxide): δ 8·31 (m, 1 H, 8-H), 7·00—7·70 (m, 9 H, Ar—H). Mass spectrum: *m/e* 318 (M^+, $C_{18}H_{14}N_4O_2$).

V and *VI*: *Ib* (7·21 g, 0·02 mol), 40 ml of hydrazine hydrate, reflux for 4 h, procedure *B*. The crude product was crystallized, yield 6·3 g (84%) of compound *V*. IR spectrum (KBr). 1 520 (NH, amide), 1 590 (Ar), 1 630 (CO, amide), 3 200—3 300 cm^{-1} (NH_2, NH, OH). ^1H NMR spectrum (hexadeuterodimethyl sulphoxide): δ 8·21 (bs, 1 H, $C_{(8)}$—H), 7·30 (m, 6 H, Ar—H), 2·80 (q, J = 7·0 Hz, 2 H, $ArCH_2$), 2·70 (q, J = 7·0 Hz, 2 H, $ArCH_2$). 1·27 (t, J = 7·0 Hz, 3 H, $ArCH_2$—CH_3), 1·25 (t, J = 7·0 Hz, 3 H, $ArCH_2$—CH_3). Following separation of compound *V* the mother liquors were chromatographed on silica gel (30-fold weight) with chloroform as eluant. The first fractions contained 0·2 g of the compound *V*. Elution of the column with ethanol and crystallization of the combined fractions afforded compound *VI* (0·5 g, 7%). Mass spectrum: *m/e* 360, (M^+, $C_{22}H_{20}N_2O_3$).

VII: *Ia* (0·61 g, 0·002 mol), 4 ml of hydrazine hydrate, reflux for 3 h, procedure *A*. The crude product was purified by column chromatography on 16 g of silica gel, chloroform being used as eluant. Crystallization of the combined fractions yielded 0·1 g (13%) of compound *VII*. IR spectrum (KBr): 1 638, 1 600 (Ar), 1 750, 1 700 (CO), 3 350 cm^{-1} (OH, NH). ^1H NMR spectrum (hexadeuterodimethyl sulphoxide): δ 11·25 (bs, 1 H, OH), 8·45 (bs, 1 H, NH), 8·50 (m, 1 H, $C_{(8)}$—H), 6·50—7·70 (m, 13 H, ArH).

VIII and *IX*: *Ib* (7·2 g, 0·02 mol) 40 ml) of *IIIa*, reflux for 3 h, procedure *C*. The oily layer was extracted into three 100 ml portions of chloroform. The combined chloroform portions were shaken with 200 ml of water, taken to dryness and chromatographed on 350 g of silica gel (elution with benzene containing 10% of chloroform). Following elution of yellow dyes, compound *IX* was obtained (5·7 g, 63%). IR spectrum (chloroform): 1 600 (Ar), 1 715, 1 760 (CO), 3 360 (cm^{-1} (NH). ^1H NMR spectrum (deuteriochloroform): δ 8·20 (d, J = 2·0 Hz, 1 H, $C_{(8)}$—H), 7·62 (d, J = 8·5 Hz, 1 H, $C_{(5)}$—H), 7·38 (dd, J = 8·5, 2·0 Hz, 1 H, $C_{(6)}$—H), 7·19 (s, 4 H, ArH), 6·60—7·15 (m, 5 H, ArH), 6·10 (bs, 1 H, NH), 4·39 (s, 3 H, $ArOCH_3$), 2·80 (q, J = 7·0 Hz, 2 H, $ArCH_2$), 2·70 (q, J = 7·0 Hz, 2 H, $ArCH_2$), 1·29 (t, J = 7·0 Hz, 3 H, $ArCH_2$—CH_3), 1·27 (t, J = 7·0 Hz, 3 H, $ArCH_2$—CH_3).

Further chromatographic fractions contained compound *VIII*, yield after crystallization 1·38 g (16%). IR spectrum (chloroform): 1 610 (Ar), 1 705, 1 770 (CO), 3 370 (NH), 3 430 cm^{-1} (OH). ^1H NMR spectrum (deuteriochloroform): δ 8·70 (bs, 1 H, OH), 8·20 (d, J = 2·0 Hz, 1 H, $C_{(8)}$—H), 7·71 (d, J = 8·5 Hz, 1 H, $C_{(5)}$—H), 7·40 (*dd*, J = 8·5, 2·0 Hz, 1 H, $C_{(6)}$—H), 7·20 (s, 4 H, ArH), 6·60—7·20 (m, 5 H, ArH), 6·20 (bs, 1 H, NH), 2·82 (q, J = 7·0 Hz, 2 H, $ArCH_2$), 2·80 (q, J = 7·0 Hz, 2 H, $ArCH_2$), 1·30 (t, J = 7·0 Hz, 3 H, $ArCH_2$—CH_3), 1·27 (t, J = 7·0 Hz, 3 H, $ArCH_2$—CH_3). Mass spectrum: *m/e* 436 (M^+, $C_{28}Z_{24}N_2O_3$).

X: *Ib* (9·01 g, 0·025 mol), 5·44 g of *IIIb* (0·0275 mol), 100 ml of toluene, reflux for 10 h, procedure *C*. The crude product was taken into three 50 ml portions of chloroform, taken to dryness and crystallized; yield 9·4 (87%) of compound *X*. IR spectrum (chloroform): 1 345, 1 525 (NO_2), 1 510, 1 600, 1 620 (Ar), 1 730, 1 770 (CO), 3 370 cm^{-1} (NH). ^1H NMR spectrum (deuteriochloroform): δ 9·60 (s, 1 H, NH), 9·02 (d, J = 2·0 Hz, 1 H, $C_{(9)}$—H), 8·22 (d, J = 2·0 Hz, 1 H, $C_{(8)}$—H), 8·18 (dd, J = 8·5 Hz, 2·0 Hz, 1 H, $C_{(11)}$—H), 7·70 (d, J = 8·5 Hz, 1 H, $C_{(5)}$—H), 7·42 (dd, J = 8·5, 2·0 Hz, 1 H, $C_{(6)}$—H), 7·30, 7·15 (ABq, J = 8·5 Hz, 4 H, *p*-substituted Ar), 6·88 (*d*, J = 8·5 Hz, 1 H, $C_{(12)}$—H), 4·40 (s, 3 H, $ArOCH_3$), 2·80 (q, J = 7·0 Hz, 2 H, $ArCH_2$), 2·70 (q, J = 7·0 Hz, 2 H, $ArCH_2$), 1·29 (t, J = 7·0 Hz, 3 H, $ArCH_2$—CH_3), 1·25 (t, J = 7·0 Hz, 3 H, $ArCH_2CH_3$).

XI: *IIa* (0·58 g, 0·002 mol), 8 ml of hydrazine hydrate (103%), reflux for 16 h, procedure *A*. Yield 0·32 g (55·1%). IR spectrum (KBr): 1528 (Ar), 1 580 (NH-amide), 1 635 (CO-amide), 3 180 cm^{-1} (NH). Mass spectrum: *m/e* 290 (M^+, $C_{18}H_{14}N_2O_2$).

XII: *IIb* (0·56 g, 0·002 mol), 8 ml hydrazine hydrate (103%), reflux 16 h, procedure *A*. Yield 0·21 g (36%). IR spectrum (KBr): 1 510, 1 610 (Ar), 1 582 (NH, amide), 1 650 (CO, amide), 3 360 cm^{-1} (NH). Mass spectrum: *m/e* 290 (M^+, $C_{18}H_{14}N_2O_2$).

XIII: *IIc* (6·92 g, 0·002 mol) 15 ml of hydrazine hydrate (103%), reflux for 16 h, procedure *A*. Two-fold crystallization yielded 2·0 g (29%) of compound *XIII*. IR spectrum (KBr): 1 580 (Ar), 1 648 cm^{-1}, (CO-amide), ^1H NMR spectrum (hexadeuterodimethyl sulphoxide): δ 10·02 (bs, 1 H, OH), 8·03 (bs, 1 H, $C_{(8)}$—H), 7·20—7·50 (m, 2 H, $C_{(6)}$—H, $C_{(5)}$—H), 7·18, 7·03 (ABq, J = 8·5 Hz, 4 H, *para*-substituted Ar), 4·80 (bs, 2 H, NH_2), 2·65 (q, J = 7·0 Hz, 2 H, $ArCH_2$), 2·60 (q, J = = 7·0 Hz, 2 H, $ArCH_2$), 1·21 (t, J = 7·0 Hz, 3 H, $ArCH_2$—CH_3), 1·18 (t, J = 7·0 Hz, 3 H, $ArCH_2$—CH_3).

Elemental analyses were carried out by Mrs J. Komancová and Mrs J. Kropáčová of the Analytical Department (head Dr J. Körbl), the antineoplastic effects were assessed by Mrs S. Pokorná of the Pharmacological Department (head Dr K. Řežábek).

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