# SOME DERIVATIVES OF 4-ARYL-2,3-DICYANO-1-NAPHTHOL*

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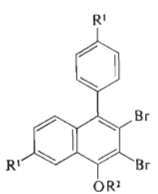
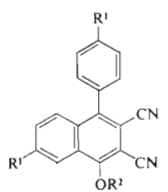
Reactions of vicinal aromatic dibromo derivatives *Ia—d* with the system copper(I) cyanide–tetramethylurea gave the vicinal dicyano derivatives *IIa—d*; products of partial substitution, *Va—d*, demethylation and deacetylation, *IIIa—c*, were also formed. The compounds *IIIa—c* were also prepared by direct demethylation of compounds *IIa—c* with the system. anhydrous aluminium chloride–dichloroethane. The structures of selected compounds were determined by spectral methods. Compounds *IIa—d* have proved to have a moderate antineoplastic effect in animals with some transplantable experimental tumours.

Within the framework of our search for antineoplastic compounds we have recently described syntheses[1,2] of some 4-aryl-2,3-dihalogeno-1-naphthol derivatives, whose structural similarity to the podophyllotoxin type lignanes and easy accessibility proved useful for syntheses of model compounds and for the study of antineoplastic effects.

The present paper deals with the replacement of the vicinal bromine atoms in derivatives of 4-aryl-2,3-dibromo-1-naphthol[1,2], *Ia – d*, by nitrile groups, in order to obtain derivatives of 4-aryl-2,3-dicyano-1-naphthol (*IIa – d*, *IIIa – c*, see Table I).




*Ia*, $R^1 = H$, $R^2 = CH_3$
*Ib*, $R^1 = CH_3$, $R^2 = CH_3$
*Ic*, $R^1 = C_2H_5$, $R^2 = CH_3$
*Id*, $R^1 = C_2H_5$, $R^2 = COCH_3$

*IIa*, $R^1 = H$, $R^2 = CH_3$
*IIb*, $R^1 = CH_3$, $R^2 = CH_3$
*IIc*, $R^1 = C_2H_5$, $R^2 = CH_3$
*IId*, $R^1 = C_2H_5$, $R^2 = COCH_3$

*IIIa*, $R^1 = R^2 = H$
*IIIb*, $R^1 = CH_3$, $R^2 = H$
*IIIc*, $R^1 = C_2H_5$, $R^2 = H$

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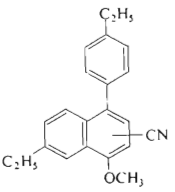
To find a suitable nitrilation method we chose compound *Ic* and copper(I) cyanide (CuCN) in pyridine[3,4], quinoline[5] or in melt[6]. The reaction of *Ic* with CuCN in quinoline at 180–220°C gave compound *IV*; the reaction mixture also contained some decomposition products and the unreacted compound *Ic*. The $^1$H-NMR spectrum of the compound *IV* did not enable us to determine the position of the nitrile group.

TABLE I
Nitrilation Products of 4-Aryl-2,3-dibromo-1-naphthol Derivatives

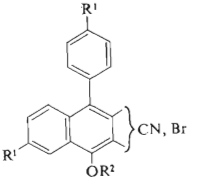
| Compound | $R^1$ $R^2$ | Formula (mol. mass) | M.p., °C (solvent) | Calculated/Found | | | |
|---|---|---|---|---|---|---|---|
| | | | | % C | % H | % N | % Br |
| *IIa* | H | $C_{19}H_{12}N_2O$ | 198—200 | 80·26 | 4·26 | 9·85 | — |
| | $CH_3$ | (284·3) | (chloroform) | 80·37 | 4·47 | 10·05 | — |
| *IIb* | $CH_3$ | $C_{21}H_{16}N_2O$ | 179—181 | 80·74 | 5·16 | 8·97 | — |
| | $CH_3$ | (312·4) | (benzene) | 80·95 | 5·26 | 8·80 | — |
| *IIc* | $C_2H_5$ | $C_{23}H_{20}N_2O$ | 161—163 | 81·15 | 5·92 | 8·23 | — |
| | $CH_3$ | (340·4) | (chloroform) | 80·88 | 6·14 | 8·11 | — |
| *IId* | $C_2H_5$ | $C_{24}H_{20}N_2O_2$ | 171—173 | 78·24 | 5·47 | 7·60 | — |
| | $COCH_3$ | (368·4) | (methanol) | 78·24 | 5·31 | 7·36 | — |
| *IIIa* | H | $C_{18}H_{10}N_2O$ | 268—270 | 79·98 | 3·72 | 10·36 | — |
| | H | (270·3) | (chloroform) | 79·82 | 3·63 | 10·29 | — |
| *IIIb* | $CH_3$ | $C_{20}H_{14}N_2O$ | 278—280 | 80·52 | 4·73 | 9·36 | — |
| | H | (298·4) | (benzene) | 80·24 | 4·70 | 9·17 | — |
| *IIIc* | $C_2H_5$ | $C_{22}H_{18}N_2O$ | 234—236 | 80·96 | 5·55 | 8·58 | — |
| | H | (326·4) | (chloroform) | 80·74 | 5·65 | 8·53 | — |
| *IV* | $C_2H_5$ | $C_{22}H_{21}NO$ | 132—133 | 83·78 | 6·71 | 4·44 | — |
| | $CH_3$ | (315·4) | (hexane) | 83·98 | 7·04 | 4·15 | — |
| *Va* | H | $C_{18}H_{12}BrNO$ | [a] | 63·92 | 3·58 | 4·14 | 23·63 |
| | $CH_3$ | (338·2) | | 64·11 | 3·75 | 4·28 | 24·00 |
| *Vb* | $CH_3$ | $C_{20}H_{16}BrNO$ | [a] | 65·58 | 4·40 | 3·82 | 21·82 |
| | $CH_3$ | (366·3) | | 65·38 | 4·21 | 3·61 | 22·02 |
| *Vc* | $C_2H_5$ | $C_{22}H_{20}BrNO$ | [a] | 67·13 | 5·11 | 3·55 | 20·25 |
| | $CH_3$ | (394·3) | | 67·12 | 5·15 | 3·50 | 20·19 |
| *Vd* | $C_2H_5$ | $C_{23}H_{20}BrNO_2$ | [a] | 65·41 | 4·77 | 3·32 | 18·92 |
| | $COCH_3$ | (422·3) | | 65·23 | 4·95 | 3·35 | 18·66 |

[a] Mixture of position isomers.

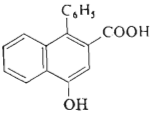
In the system CuCN–pyridine only a trace of the compound *IV* was formed. The melting of *Ic* with CuCN at 160 to 220°C produced a mixture, from which *c.* 10% of compound *IIc* was isolated. Changes in temperature, proportion of the components and time did not lead to a higher yield. In the use of CuCN in boiling dimethyl sulphoxide[7] or hexamethylphosphorus triamide we isolated a product of partial substitution, *Vc* ( a mixture of position isomers) and decomposition products. Only in the system CuCN–tetramethylurea did we obtain the compound *IIc* in a yield of 65–70%, the identified by-products being *IIIc* and *Vc*. In the same way we converted compounds *Ia,b,d* into the corresponding *IIa,b,d*, the by-products being *IIIa–c* and *Va,b,d*. The nitrilation system proved good for substitutions in vicinal aromatic dibromo derivatives; attempted nitrilation of 4-phenyl-2,3-dichloro--1-methoxynaphthalene[2] (*VI*) gave only a trace amount of compound *IIa*.




*IV*




*Va*, $R^1 = H$, $R^2 = CH_3$
*Vb*, $R^1 = R^2 = CH_3$
*Vc*, $R^1 = C_2H_5$, $R^2 = CH_3$
*Vd*, $R^1 = C_2H_5$, $R^2 = COCH_3$




*VII*

The role of N,N,N′,N′-tetramethylurea does not consist just in creating a suitable medium; it also solvates CuCN and forms of a copper complex, in which participates the halogen atom of the aryl halide and molecules of N,N,N′,N′-tetramethyl--urea, forming ligands of the complex, like, *e.g.*, in the system CuCN–dimethylformamide[7,8]. On the basis of electronegativity of the halogens in the aryl halides the tendency of bromine to form a complex with CuCN is greater than that of chlorine, in keeping with the reported[7] and our results. Nitrilation of the vicinal dihalogen derivatives was effected with the system CuCN–dimethylformamide[7–9] or CuCN–N-methylpyrrolidone[10]. These systems were examined with the compound *Ia*. The products were the same as in the use of the system CuCN–N,N,N′,N′--tetramethylurea, but the main product was *Va*, resulting from a partial substitution (mixture of position isomers). The ready formation of the nitrilation complex in the case of N,N,N′.N′-tetramethylurea may to some extent be due to its high solvation power and suitable physico-chemical properties[11].

Compounds *IIIa–c*, which arise as nitrilation by-products but are difficult to isolate, were prepared from compounds *IIa–c* by demethylation with anhydrous aluminium chloride in 1,2-dichloroethane at 20–25°C (modification of the procedure in ref.[12]). The yield was almost quantitative if 3 mol equivalents of aluminium chloride were used. Other demethylation methods, with, *e.g.*, alkaline or acid agents in polar media, led to destruction of the nitrile groups. Thus reaction of *IIa* with 48% hydrobromic acid in acetic acid gave rise to a mixture containing compound *VII* as the main product. The position of the carboxyl group was determined from the IR spectrum on the basis of position of the carboxyl peak at 1 700 $cm^{-1}$. If the naphthalene ring had been *ortho*-substituted in respect to the hydroxy group the carboxyl peak would have been shifted to a lower frequency (*c.* 1 660–1 670 $cm^{-1}$), due to the formation of a hydrogen bond.

The structures of selected compounds were confirmed by IR and $^1$H-NMR spectra. The presence of nitrile groups in the compounds of types *II*, *III* and *V* was demonstrated by a band in the IR spectra at 2230 to 2250 $cm^{-1}$. The $^1$H-NMR spectra of compounds *V*, exhibiting doubled signals of the $OCH_3$ group, prove them to be mixture of position isomers.

As to the antineoplastic action, compounds *IIa–d* exhibited a moderate effect in animals with experimental tumours. The best result was observed with *IIc*, which, when administered orally in a dose of 100 mg/kg, reduced the size of tumours in mice with mammary adenocarcinoma HK by 35% and extended survival by 20%. In a dose of 200 mg/kg it reduced tumours S 37 by 20% and extended survival of rats with the Yoshida tumour by 21%.

## EXPERIMENTAL

The melting points of the compounds were determined on the Kofler block and are not corrected. The samples for elemental analyses were dried at temperatures corresponding to their melting points over phosphorus pentoxide at a pressure of 70 Pa. The homogeneity of the samples and composition of the reaction mixtures were followed by TLC using reflex foils Silufol $UV_{254}$ (Kavalier) by means of quenching of UV light at 254 nm. The reaction mixtures were resolved by column chromatography on Kieselgel 60 reinst (Merck). $^1$H-NMR spectra were measured with an apparatus Tesla BS487C (80 Hz), the spectra with the designation 60 MHz were measured with an apparatus ZKR 60 Zeiss Jena in 10% solutions, TMS being used as internal standard. The IR spectra were measured with spectrometers Perkin–Elmer 577 and Infrascan-Hilger.

### Nitrilation of Derivatives *Ia—c* with the System CuCN–N,N,N′,N′-Tetramethylurea

To a suspension of 3—4 mol equivalents of CuCN in N,N,N′,N′-tetramethylurea, prepared at room temperature, was added 1 mol equivalent of compound *Ia—c* (refs[1,2]) and the mixture was heated for 3 to 6 h to 150—160°C. The N,N,N′,N′-tetramethylurea was then distilled off under reduced pressure (5—6 kPa) and the product was decomposed by boiling for 2 h in benzene or toluene containing 10 to 30% (v/v) of methanol or ethanol. After cooling the solid portion was collected

on a filter and boiled again in a half amount of the same mixture. The combined filtrates were concentrated to a syrupy consistence. After an addition of methanol the separated product was collected on a filter (mixtures of compounds *IIa—c* and *Va—c*) and the individual compounds were isolated by crystallization or column chromatography.

*Compounds* IIa *and* Va: 156·8 g (0·4 mol) of *Ia*, 112·4 g (1·24 mol) of CuCN, 500 ml of tetramethylurea, reflux for 3 h, decomposition with 1300 ml and 600 ml of a toluene–ethanol mixture. Compound *IIa* was isolated by crystallization (79 g, 70%), compound *Va* by column chromatography of the mother liquor with benzene as eluant; yield 15 g (11%). *Va*: $^1$H-NMR spectrum ($CDCl_3$): $\delta$ 8·15 (m, 1 H, 8-H); 7·10—7·70 (m, 8 H, Ar—H); 4·04, 4·00 ($\sum$ 3 H, $OCH_3$). IR spectrum (5% $CHCl_3$): 2860 ($OCH_3$), 2240 (CN), 1615, 1578, 1550 $cm^{-1}$ (Ar).

*Compounds* IIb *and* Vb: 4·20 g (0·01 mol) of *Ib*, 2·68 g (0·03 mol) of CuCN, 10 ml of tetramethylurea, reflux for 4 h, decomposition with 50 and 25 ml of a benzene–methanol mixture. The crude product was resolved by column chromatography (tetrachloromethane–benzene 7 : 3). The first fractions contained compound *Vb* (0·1 g, 27·3%). Compound *IIb* was eluted with benzene (1·1 g, 35·2%). *IIb*: $^1$H-NMR spectrum ($CDCl_3$): $\delta$ 8·10 (mcs, $J$ = 1·5 Hz, 1 H, 8-H); 7·62 (d, $J$ = 8·0 Hz, 1 H, 5 H); 7·46 (mcd, $J$ = 8·0, 1·5 Hz, 1 H, 6-H); 7·38 (d, $J$ = 8·0 Hz, 2 H, Ar—H); 7·21 (d, $J$ = 8·0 Hz, 2 H, Ar—H); 4·35 (s, 3 H, $OCH_3$); 2·58 (s, 3 H, Ar—$CH_3$); 2·42 (s, 3 H, Ar—$CH_3$). IR spectrum (5% $CHCl_3$): 2230 (CN), 1620, 1573, 1520 (Ar), 825 $cm^{-1}$ (*para*-substituted Ar).

*Compound* IIc *and* Vc: 86·4 g (0·192 mol) of *Ic*, 54·0 g (0·6 mol) of CuCN, 300 ml of tetramethylurea, reflux for 4 h, decomposition with two 600 ml portions of a system benzene–methanol. The mixture of *IIc* and *Vc* was resolved by column chromatography (tetrachloromethane); yields 44·7 g (68%) of *IIc* and 5·3 g (7%) of *Vc*. *IIc*: $^1$H-NMR spectrum (60 MHz) ($CDCl_3$): $\delta$ 8·05 (bs, 1 H, 8-H); 7·10—7·70 (m, 6 H, Ar—H); 4·30 (s, 3 H, $OCH_3$); 2·85 (q, $J$ = 6·5 Hz, 2 H, Ar—$CH_2$); 2·70 (q, $J$ = 6·5 Hz, 2 H, Ar—$CH_2$); 1·30 (t, $J$ 6·5 Hz, 6 H, $CH_2$—$CH_3$). *Vc*: $^1$H-NMR spectrum (60 MHz) ($CDCl_3$): $\delta$ 8·04 (bs, 1 H, 8-H); 7·20—7·70 m (6 H); 3·95 (s, 3 H, $OCH_3$); 2·82 (q, $J$ = 6·5 Hz, 2 H, Ar—$CH_2$); 2·70 (q, $J$ = 6·5 Hz, 2 H, Ar—$CH_2$); 1·30 (t, $J$ = 6·5 Hz, 6 H, $CH_2CH_3$).

## Nitrilation of Compound *Id*

To a suspension of 1·79 g (0·02 mol) of CuCN in 7 ml of tetramethylurea was added 2·4 g (0·005 mol) of *Id* (ref.[2]) and the mixture was heated for 4·5 h to 150—160°C. After distilling off the solvent the residue was decomposed by boiling in 40 ml of chloroform and the solid was collected on a filter. The filtrate was concentrated, dissolved in a benzene–cyclohexane mixture (1 : 1) and chromatographed. The first fractions contained compound *Vd* (150 mg, 7·6%), further fractions compound *IId* (330 mg, 18%). Compound *IIc* (530 mg, 32·5%) was then eluted with benzene containing 10% of ethanol. *IId*: $^1$H-NMR spectrum: $\delta$ 7·20—7·90 (m, 7 H, Ar—H), 2·85 (q, $J$ = 6·5 Hz, 2 H, Ar—$CH_2$); 2·75 (q, $J$ = 6·5 Hz, 2 H, Ar—$CH_2$); 2·60 (s, 3 H, $OCOCH_3$); 1·35 (t, $J$ = 6·5 Hz, 6 H, $CH_2$—$CH_3$). IR spectrum (KBr): 2250 (CN), 1788 (Ar—$OCOCH_3$),: 1620, 1585 (Ar), 1520, 840 (*para*-substituted Ar), 873 $cm^{-1}$ (1,2,4-trisubstituted Ar). *IIIc* $^1$H-NMR spectrum (hexadeuteriodimethyl sulphoxide): $\delta$ 8·20 (bs, 1 H, OH); 7·10—7·70 (m, 7 H, Ar—H); 2·75 (q, $J$ = 6·5 Hz, 2 H, Ar—$CH_2$); 2·65 (q, $J$ = 6·5 Hz, 2 H, Ar—$CH_2$); 1·31 (t, $J$ = 6·5 Hz, 3 H, $CH_2$—$CH_3$); 1·29 (t, $J$ = 6·5 Hz, 3 H, $CH_2$—$CH_3$). IR spectrum (KBr): 3260 (OH), 2250 (CN), 1623, 1575 (Ar) 1520, 840 (*para*-substituted Ar), 873 $cm^{-1}$ (1,2,4-trisubstituted Ar). *Vd*: $^1$H-NMR spectrum ($CDCl_3$): $\delta$ 7·20—7·80 (m, 7 H, Ar—H); 2·82 (q, $J$ = 6·5 Hz, 2 H, Ar—$CH_2$); 2·73 (q, $J$ = 6·5 Hz, 2 H, Ar—$CH_2$); 2·55 (s, 3 H, $OCOCH_3$); 1·31 (t, $J$ = 6·5 Hz, 3 H, $CH_2$—$CH_3$); 1·29 (t, $J$ = 6·5 Hz, 3 H, $CH_2$—$CH_3$). IR spectrum (KBr):

2255 (CN), 1784 (Ar $OCOCH_3$) 1628, 1586, 1560 (Ar), 1520, 840 (*para*-substituted Ar), 869 $cm^{-1}$ (1,2,4-trisubstituted Ar).

Demethylation of Compounds *IIa—c*

To a solution of 1 mol equivalent of compound *IIa—c* in dichloroethane were added 3 mol equivalents of anhydrous aluminium chloride and the mixture was stirred at 20—25°C. The dichloroethane was distilled off and the residue was decomposed with a mixture of ice and concentrated hydrochloric acid (1 : 1). The precipitate was collected on a filter, washed with water and dried. The crude products were purified by crystallization.

*Compound* IIIa: 28·4 g (0·1 mol) of *IIa*, 600 ml of dichloroethane, 40 g (0·3 mol) of anhydrous aluminium chloride, 3h; yield 23 g (85%). $^1$H-NMR spectrum (hexadeuteriodimethyl sulphoxide): $\delta$ 8·40 (m, 1 H, 8-H); 7·20—7·90 (m, 8 H, Ar—H). IR spectrum (KBr): 2210 (CN), 1580 $cm^{-1}$ (Ar).

*Compound* IIIb: 3·12 g (0·01 mol) of *IIb*, 50 ml of dichloroethane, 4·0 g (0·03 mol) of anhydrous aluminium chloride, 8 h; yield 2·4 g (81%). $^1$H-NMR spectrum (hexadeuteriodimethyl sulphoxide): $\delta$ 8·15 (bs, 1 H, 8-H); 7·10—7·60 (m, 6 H, Ar-H); 2·48 (s, 3 H, Ar—$CH_3$); 2·39 (s, 3 H, Ar—$CH_3$).

*Compound* IIIc: 340 mg (0·001 mol) of *IIc*, 6 ml of dichloroethane, 400 mg (0·003 mol) of anhydrous aluminium chloride, 9 h; yield 281 mg (86%).

Nitrilation of Compound *Ic* with the System CuCN–Quinoline

A mixture of *Ic* (2·2 g, 0·005 mol), CuCN (1·0 g, 0·011 mol) and quinoline (1·5 ml) was heated to 200°C for 5 h. After cooling it was stirred in chloroform (50 ml), the solid was filtered off and the filtrate was concentrated and purified by column chromatography, benzene–cyclohexane (1 : 1) being used as eluant; yield 230 mg (14·6%) of compound *IV*. $^1$H-NMR spectrum (60 MHz) ($CDCl_3$): $\delta$ 8·09 (bs, 1 H, 8-H); 7·20—7·70 m (6 H); 6·85 (s, 1 H, 2-H or 3-H); 3·93 (s, 3 H, $OCH_3$); 2·82 (q, $J$ = 6·5 Hz, 2 H, Ar—$CH_2$); 2·70 (q, $J$ = 6·5 Hz, 2 H, Ar—$CH_2$); 1·30 (t, $J$ = 6·5 Hz, 6 H, $CH_2$—$CH_3$).

Demethylation of Compound *IIa* with Hydrobromic Acid

To a boiling solution of *IIa* (1·0 g, 0·035 mol) in 20 ml of acetic acid was added dropwise, in the course of 1 h, 15 ml of 48% hydrobromic acid and the mixture was refluxed for 8 h. After cooling the separated substance was collected on a filter and recrystallized from benzene; yield 300 mg (32·6%), m.p. 214—216°C (benzene). For $C_{17}H_{12}O_3$ (264·3) calculated: 77·26% C, 4·57% H; found: 77·04% C, 4·36% H. $^1$H-NMR spectrum (hexadeuteriodimethyl sulphoxide): $\delta$ 10·45 (bs, 1 H, OH); 8·15 (m, 1 H, 8-H); 7·00—7·40 (m, 9 H, Ar—H). IR spectrum (KBr): 2600, (COOH) 1700 (COOH), 1580 $cm^{-1}$ (Ar).

*The elemental analyses were carried out by Mrs J. Komancová of the Analytical Department of the Institute (head Dr J. Körbl). The antineoplastic effects were evaluated by Dr K. Řežábek and coworkers of the Pharmacological Department (head Dr K. Řežábek).*

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