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Synthesis of Naphthoxazole Derivatives by the Application of the Vilsmeier–Haack Reaction: Part II. 2-Hetarylnaphth[1,2-*d*]oxazole Derivatives

S. Seshadri, M. R. Jayant, R. Krishnan and P. C. Shekar

Dyes Research Laboratory, Department of Chemical Technology, University of Bombay, Matunga, Bombay 400 019, India

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SUMMARY

The Vilsmeier–Haack Reaction has been utilised for the synthesis of substituted naphth[1,2-d]oxazolylmalondialdehydes with substituents at the 4- or 5- positions. The malondialdehydes were converted to various hetarylnaphthoxazoles. It was found that the 2-hetarylnaphthoxazoles with 3-carboxyl derived substituents have intense emission properties.

1 INTRODUCTION

In a previous publication,[1] we have described the synthesis of 2-hetarylnaphth[1,2-*d*]oxazole derivatives. It was observed that the fluorescence characteristics of the heterocyclic derivatives was not adequate for practical purposes. It was therefore of interest to incorporate suitable substituents into the naphthalene moiety in order to enhance the fluorescence characteristics.

The present paper describes the synthesis of 2-hetarylnaphth[1,2-*d*]oxazole derivatives containing 5-cyano, 5-acetamido and 4-carbonyl derived substituents.

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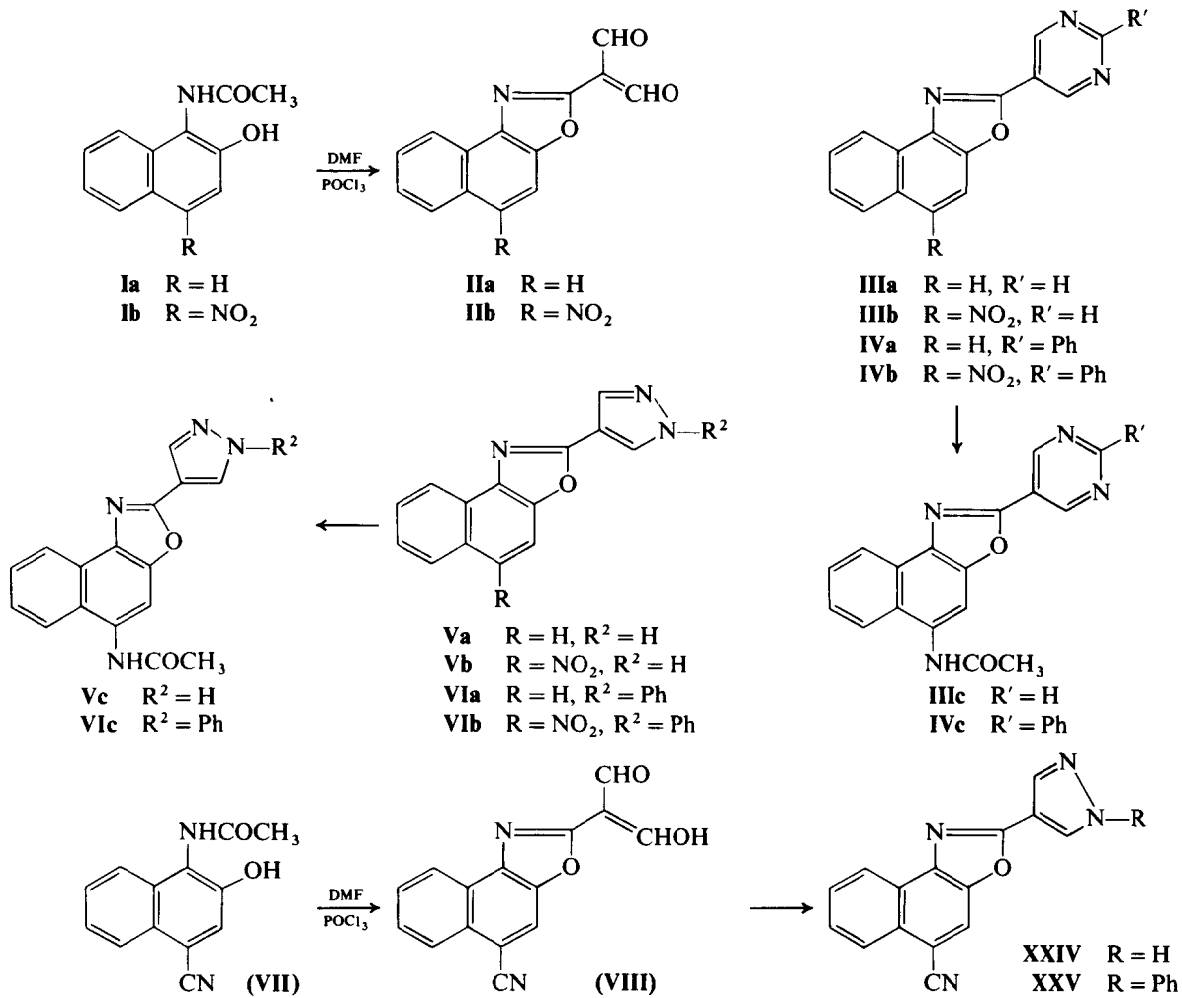
2 RESULTS

The 5-substituted compounds were derived as indicated in Scheme 1. Thus the nitro derivative was obtained by the known sequence of nitration of 1-acetamido-2-naphthol and subsequent Vilsmeier formylation of the derived acetamido compound. The 5-nitronaphthoxazolylmalondialdehyde was converted to the 2-pyrimidyl and 2-pyrazolyl derivatives, which were then reductively acylated to the 5-acetamido derivatives.

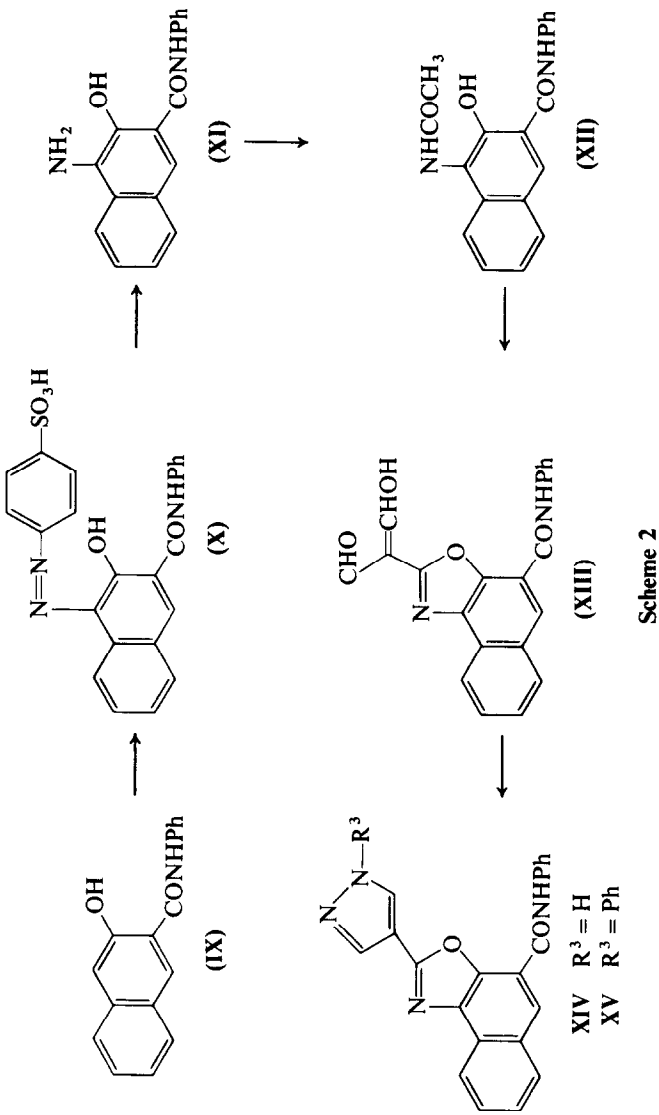
The weak fluorescence obtained even with an added auxochromic acetamido group led us to study the effect of a 5-cyano substituent. The starting material for such a compound, namely 1-acetamido-4-cyano-2-naphthol, was obtained according to literature procedures by reductive cyanation of 1-nitroso-2-naphthol followed by acetylation. Vilsmeier formylation of the cyano compound (**VII**) gave the desired malondialdehyde (**VIII**), which was utilised for the synthesis of 2-hetaryl-5-cyanonaphth[1,2-*d*]oxazoles. The 5-cyano substituted compounds, however, failed to show improved fluorescence.

The effect of a 4-substituent in the naphth[1,2-*d*]oxazole derivatives on the fluorescence characteristics was then studied. The synthesis of such compounds is rendered facile because of the commercial availability of 2-hydroxy-3-naphthoic acid and its derivatives. 1-Acetamido-3-phenylcarbamoyl-2-naphthol (**XII**) was obtained by the route shown in Scheme 2. Vilsmeier formylation of **XII** gave the expected malondialdehyde (**XIII**) which readily reacted with hydrazine and phenyl hydrazine to yield the respective 2-pyrazolyl derivatives. The 4-substituted 2-pyrazolyl naphth[1,2-*d*]oxazoles thus obtained showed much stronger fluorescence than the 5-substituted derivatives.

The influence of other substituents at the 4-position on the fluorescence of the derived naphthoxazoles was therefore investigated. Thus, 1-acetamido-2-hydroxy-3-naphthoic acid methyl ester was synthesised by nitration of 2-hydroxy-3-naphthoic acid methyl ester, reduction and acetylation (Scheme 3). Vilsmeier reaction of this gave, on the usual alkaline work-up, the naphthoxazolylmalondialdehyde (**XX**) with a COOH group at the 4-position. Reaction of **XX** with hydrazine and phenylhydrazine gave the 2-pyrazolyl-4-carboxylic acid derivatives (**XXI** and **XXII**). Subsequent esterification of **XXII** with methanolic HCl gave the methyl ester **XXIII**. These compounds also showed significant fluorescence emission properties, with the ester derivative giving the best performance in the whole group. The UV absorption and fluorescence emission data are reported in Table 1. Whilst some of the compounds were fairly efficient with reference to the standard commercial whitener, the compounds were not, however, satisfactory when applied as whiteners on polyester fabric.


NHCOCH3
OH
R
DMF
POCl3
CHO
CHO
N
O
R
Ia R = H
Ib R = NO2
IIa R = H
IIb R = NO2
R'
N
N
IIIa R = H, R' = H
IIIb R = NO2, R' = H
IVa R = H, R' = Ph
IVb R = NO2, R' = Ph
N—R2
Va R = H, R2 = H
Vb R = NO2, R2 = H
VIa R = H, R2 = Ph
VIb R = NO2, R2 = Ph
Vc R2 = H
VIc R2 = Ph
IIIc R' = H
IVc R' = Ph
CHOH
CN
(VII)
(VIII)
XXIV R = H
XXV R = Ph

Scheme 1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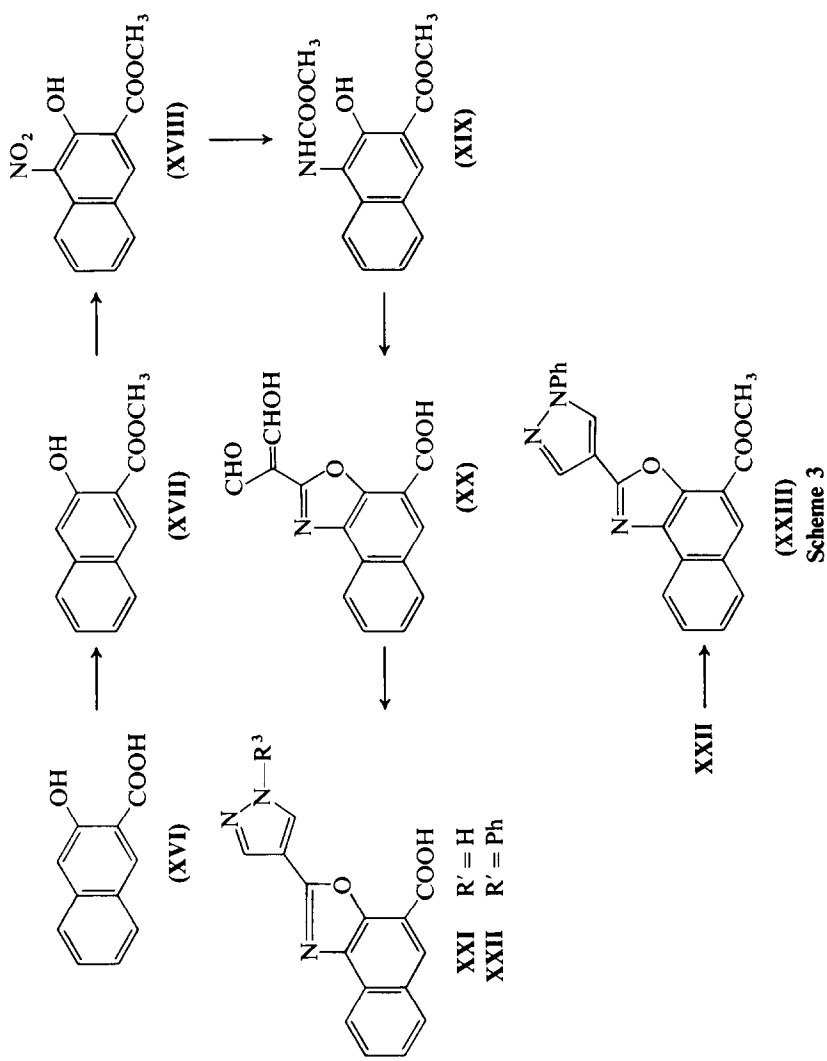
CONHPh
(IX)
SO3H
N=N
OH
CONHPh
(X)
NH2
OH
CONHPh
(XI)
NHCOCH3
OH
CONHPh
(XII)
CHO
CHOH
O
N
CONHPh
(XIII)
N
N—R3
O
N
CONHPh
XIV R3 = H
XV R3 = Ph

Scheme 2


NO2
OH
COOCH3
(XVIII)
NHCOOCH3
OH
COOCH3
(XIX)
OH
COOCH3
(XVII)
CHO
CHOH
COOH
(XX)
NPh
COOCH3
(XXIII)
XXII
OH
COOH
(XVI)
R3
COOH
XXI R' = H
XXII R' = Ph

Scheme 3

TABLE 1
The UV Absorption and Fluorescent Emission Data[a]

Compound	λ_{max} (*nm*)	(*log* ε)	λ^{Exc} (*nm*)	λ^{Emi} (*nm*)	*Q* (*mg*)
Uvitex ERN (standard)	375	(4·61)	375	460	0·639 4
IIIa	343	(3·92)	350	435	2·486
IIIb	445	(4·16)	360	430	3·940
IIIc	322	(4·07)	370	455	5·000
IVa	356	(4·33)	370	455	1·629
IVb	355	(4·40)	374	450–455	1·601
IVc	353	(4.47)	376	458	2·240
XXIV	350	(4·11)	350	392	1·857
XXV	360	(3·79)	366	402	5·652
XIV	346	(3·93)	—	392	0·44
XV	351	(4·39)	—	398	0·38
XXI	348	(3·92)	—	391	0·48
XXII	351	(4·25)	—	395	0·39
XXIII	360	(4·19)	—	402	0·35

[a] λ_{max}, Visible absorption maximum; ε, extinction coefficient; λ^{Exc}, excitation wavelength; λ^{Emi}, emission wavelength; *Q*, weight of the compound in 100 ml methanol for an intensity of 100 units.

3 EXPERIMENTAL

All melting points are uncorrected. Several of the compounds reported gave consistently low analytical values for nitrogen (*ca* 0·5–1·0%); similar behaviour has been reported earlier.[1] **IIa, IIIa, IVa** and **Va** were prepared by the method previously reported by us.[1]

3.1 2-(Naphth[1,2-*d*]oxazolyl)malondialdehyde (IIa)

Phosphorus oxychloride (36 ml, 0·4 mol) was slowly added to dimethylformamide (30 ml, 0·4 mol) at 5–10°C with stirring. After 10 min, 1-acetamido-2-naphthol (20 g, 0·1 mol) in dimethylformamide (60 ml) was stirred into the above mixture and the solution was then heated at 70–80°C for 8 h and kept overnight at room temperature. The solution was poured into ice water (500 ml) and treated with 30% sodium hydroxide solution to pH 10–11, while the temperature of the solution was not allowed to rise above 60–70°C. The alkaline solution was heated at 60–70°C for 2 h, cooled in an ice bath and filtered. The filtrate was acidified with HCl to give a small

amount of **IIa** and the residue was extracted repeatedly with hot water to dissolve all the sodium salt of **IIa**. The filtrate from this extraction on acidification gave pure **IIa**. Yield 12 g (50%), m.p. 236–238°C. It was crystallised from dioxane in almost white crystals, m.p. 239°C.

Found: C, 70·3; H, 4·0; N, 5·5%.

$C_{14}H_9NO_3$ requires: C, 70·3; H, 3·8; N, 5·8%.

3.2 2-[2-(5-Nitronaphth[1,2-*d*]oxazolyl)]malondialdehyde (IIb)

The method of preparation was similar to that used for **IIa**, starting from **Ib**. Yield 85%, m.p. 203–205°C. It was crystallised from alcohol in brown crystals, m.p. 207°C.

Found: C, 59·5; H, 3·1; N, 9·4%.

$C_{12}H_{10}N_2O_4$ requires: C, 59·2; H, 2·8; N, 9·9%.

3.3 2-[(5-Pyrimidyl)]naphth[1,2-*d*]oxazole (IIIa)

A mixture of **IIa** (1 g) and formamide (10 ml) was refluxed for 2 h and poured into ice water. The yellowish brown solid was filtered, washed with water and dried. Yield 1 g (95%), m.p. 270–278°C. It was recrystallised from benzene–petroleum ether to give a brown product, m.p. 280°C.

Found: N, 16·6%.

$C_{15}H_9N_3O$ requires: N, 17·0%.

3.4 2-[(5-Pyrimidyl)]-5-nitronaphth[1,2-*d*]oxazole (IIIb)

This was prepared by the method used for **IIIa**, starting from **IIb**. Yield 98%, m.p. 200–202°C. It was crystallised from alcohol in light brown crystals, m.p. 204°C.

Found: N, 19·4%.

$C_{15}H_8N_4O_3$ requires: N, 19·2%.

3.5 2-[5-(2-Phenylpyrimidyl)]naphth[1,2-*d*]oxazole (IVa)

A mixture of **IIa** (1 g) and morpholine in xylene (20 ml) was refluxed for 1 h. The liquor was cooled and to the cold solution benzamidine hydrochloride (1·1 g) was added and the mixture refluxed for 1 h. On keeping the solution at room temperature overnight, crystals of **IVa** separated. Yield 1·2 g (90%), m.p. 230–235°C. Crystallisation from benzene gave light yellow crystals, m.p. 238°C.

Found: N, 12·9%.

$C_{21}H_{13}N_3O$ requires: N, 13·0%.

3.6 2-[5-(Phenylpyrimidyl)]-5-nitronaphth[1,2-*d*]oxazole (IVb)

This was prepared by the method used for **VIa**, starting from **IIb**. Yield 82%, m.p. 216–218°C. Crystallisation from alcohol gave yellow brown crystals, m.p. 220°C.

Found: N, 14·8%.

$C_{21}H_{12}N_4O_3$ requires: N, 15·2%.

3.7 2-(4-Pyrazolyl)naphth[1,2-*d*]oxazole (Va)

A mixture of **IIa** (1 g), hydrazine hydrate (0·6 ml, 80%) and methanol (20 ml) was refluxed for 1 h (until the mixture failed to give a violet colour with alcoholic $FeCl_3$) and then poured into ice water. The brown precipitate was filtered, washed with water and dried. Yield 0·98 g (99%), m.p. 278–280°C. It was crystallised from benzene in light brown crystals, m.p. 280°C.

Found: N, 17·3%.

$C_{14}H_9N_3O$ requires: N, 17·8%.

3.8 2-(4-Pyrazolyl)-5-nitronaphth[1,2-*d*]oxazole (Vb)

This was prepared by the method used for **Va**, starting from **IIb**. Yield 99%, m.p. 281–284°C. It was crystallised from alcohol in light brown crystals, m.p. 285°C.

Found N, 20·4%.

$C_{14}H_9N_3O$ requires: N, 20·0%.

3.9 2-[4-(1-Phenylpyrazolyl)]naphth[1,2-*d*]oxazole (VIa)

A mixture of **IIa** (1 g), phenylhydrazine (0·5 ml) and methanol (20 ml) was refluxed for 1 h (until the reaction mixture failed to give a violet colour with alcoholic $FeCl_3$) and poured into ice water. The brown precipitate was filtered, washed with dilute HCl and dried. Yield 0·8 g (60%), m.p. 168–174°C. It was crystallised from benzene in light yellow crystals, m.p. 175°C.

Found: C, 76·7; H, 4·2; N, 12·7%.

$C_{20}H_{13}N_3O$ requires: C, 77·2; H, 4·2; N, 13·2%.

3.10 2-[4-(1-Phenylpyrazolyl)-5-nitro]naphth[1,2-*d*]oxazole (VIb)

This was prepared by the method used for **VIa**, starting from **IIb**. Yield 80%, m.p. 239–241°C. It was crystallised from alcohol in light yellow crystals, m.p. 242°C.

Found: C, 67·7; H, 3·7; N, 16·0%.
$C_{20}H_{12}N_4O_3$ requires: C, 67·4; H, 3·4; N, 15·7%.

3.11 1-Acetamido-3-phenylcarbamoyl-2-naphthol (XII)

The red dye **X** (see Section 3.23) (47 g, 0·01 mol) was suspended in boiling acetic acid (500 ml) and zinc dust (20 g, 0·15 mol) was added in portions over 45 min. The reduction proceeded vigorously and the red colour gradually disappeared, giving finally a clear yellow solution. The solution was cooled and filtered.

To the filtrate, acetic anhydride (12 ml, 0·11 mol) was added and the liquor gently refluxed for 2 h. The solution was cooled and poured onto crushed ice (1200 g) containing hydrochloric acid (60 ml) with vigorous stirring, when a pale cream solid separated. The mixture was further stirred for 8 h and filtered. The residue obtained was dissolved in 3% sodium hydroxide solution (400 ml) and warmed at 50°C for 10 min, when a clear solution was obtained. This was filtered to remove impurity and slowly added to cooled hydrochloric acid (125 ml), when a pale cream solid precipitated. This was filtered, washed with water and dried.

Yield 23·4 g (73%), m.p. 127°C. Crystallisation from aqueous ethanol (50%) gave pale cream crystals in almost quantitative yield. It gave a violet colouration with ethanolic ferric chloride solution.

Found: C, 71·2; H, 4·8; N, 8·9%.
$C_{19}H_{16}N_2O_3$ requires: C, 71·3; H, 5·0; N, 8·8%.

3.12 Methyl ester of 1-acetamido-2-hydroxy-3-naphthoic acid (XIX)

To a suspension of methyl ester **XVIII** (see Section 3.23) (25 g, 0·1 mol) in acetic acid (125 ml) at 60°C was added zinc powder (20 g, 0·3 mol) in small portions. A vigorous reaction took place on the addition and the solution slowly turned brownish yellow. After addition of all the zinc, the mixture was heated at 60°C for 2 h, cooled and filtered.

To the filtrate, acetic anhydride (12 ml, 0·11 mol) was added and the mixture heated at 100°C for 2·5 h. The cooled solution was then poured onto crushed ice (600 g) containing hydrochloric acid (60 ml) with vigorous stirring and stirring was continued for a further 8 h. The product which separated was filtered, washed with water and dried. Yield 18·5 g (71%), m.p. 128–133°C. Crystallisation from a mixture of ethyl acetate and alcohol (1:1) gave cream crystals, m.p. 132–133°C. The crude product was satisfactory for use in further syntheses.

Found: C, 64·7; H, 5·2; N, 5·4%.
$C_{14}H_{13}NO_2$ requires: C, 64·9; H, 5·0; N, 5·4%.

3.13 2-[2-(4-Phenylcarbamoylnaphth[2,1-*d*]oxazolyl)]malondialdehyde (XIII)

Phosphoros oxychloride (62 ml, 0·4 ml) was slowly added to dimethylformamide (35 ml, 0·5 mol) at 5–10°C with stirring and to this cooled mixture was added 1-acetamido-3-phenylcarbamoyl-2-naphthol (32 g, 0·1 mol) in DMF (60 ml). After stirring for 15 min, the mixture was heated at 90–95°C for 6 h.

The reaction mixture was cooled to room temperature and poured onto ice cold water (600 ml), when a clear solution was obtained. This was treated with 25% sodium hydroxide solution to give pH 9·0 and then heated at 80°C for 2 h. It was then cooled in an ice bath and slowly added to ice cold hydrochloric acid (175 ml) with vigorous stirring, when a yellowish brown solid separated. This was filtered and the residue was extracted with hot water (3 × 100 ml), filtered and the combined filtrates added to ice cold hydrochloric acid (20 ml), when the product separated. This was filtered, washed well with water until acid-free and then dried to yield **XIII.** Yield 34 g (95%), m.p. 243–247°C. Crystallisation from a mixture of DMF and water (4:1) gave **XIII** as a deep yellow amorphous solid, m.p. 245–247°C.

Found: C, 70·2; H, 4·1; N, 7·7%.

$C_{21}H_{14}N_2O_4$ requires: C, 70·4; H, 3·9; N, 7·8%.

3.14 2-[(4-Pyrazolyl)]-4-phenylcarbamoylnaphth[1,2-*d*]oxazole (XIV)

This was prepared by the method used for **Va**, starting from **XIII**. Yield 91%, m.p. 350–354°C. Crystallisation from a mixture of DMF and methanol (1:3) gave **XIV** as pale cream needles, m.p. 352–353°C.

Found: N, 16·0%.

$C_{21}H_{14}N_4O_2$ requires: N, 15·8%.

3.15 2-[4-(1-Phenylpyrazolyl)]-4-phenylcarbamoylnaphth[1,2-*d*]oxazole (XV)

This was prepared by the method used for **Va**, starting from **XIII**. Yield 93%, m.p. 324–328°C. Crystallisation from a mixture of DMF and methanol gave pale yellow flakes of **XV** (85%), m.p. 327–328°C.

Found: N, 13·0%.

$C_{27}H_{18}N_4O_2$ requires: N, 13·0%.

3.16 2-[2-(Carboxynaphth[1,2-*d*]oxazolyl)]malondialdehyde (XX)

This was prepared by the method used for **XIII**, starting from **XIX**. Yield 92%, m.p. > 360°C. It gave a brownish violet colouration with alcoholic

ferric chloride and was soluble with effervescence in cold 5% sodium bicarbonate solution.

Found: C, 63·4; H, 3·0; N, 4·9%.

$C_{15}H_9NO_5$ requires: C, 63·6; H, 3·2; N, 5·0%.

3.17 2-(4-Pyrazolyl)-4-carboxynaphth[1,2-*d*]oxazole (XXI)

The malondialdehyde **XX** (2·8 g, 0·01 mol) was reacted with hydrazone hydrate (0·6 ml, 0·011 mol) as described for the preparation of **XV**, to afford **XXI** (2·4 g, 87%), m.p. > 360°C, as a greyish solid. Crystallisation from a mixture of DMF and methanol afforded **XXI** as a light grey solid (1·9 g, 70%), m.p. > 360°C.

Found: N, 14·8%.

$C_{15}H_9N_3O_3$ requires: N, 15·1%.

3.18 2-[4-(1-Phenylpyrazolyl)]-4-carboxynaphth[1,2-*d*]oxazole (XXII)

This was prepared from **XX** and phenylhydrazine by a method similar to that used for the preparation of **XV**. Yield 89%, m.p. 316–319°C. Crystallisation from a mixture of DMF and methanol (1 : 1) gave a light grey solid (77%), m.p. 318–319°C.

Found: N, 11·8%.

$C_{21}H_{13}N_3O_3$ requires: N, 11·8%.

3.19 Methyl ester of XXII (XXIII)

Dry hydrochloric acid gas was passed through a boiling suspension of **XXII** (1.8 g, 0·05 mol) in methanol (30 ml) for 3 h. During the esterification the product went into solution, and at the end of 3 h the solution was cooled, filtered and the filtrate diluted with 10 ml of water. The product which separated was filtered, washed with water and dried to afford the methyl ester **XXIII** (1·6 g, 85%), m.p. 153–160°C. Crystallisation from methanol gave a cream product (1·35 g, 74%), m.p. 159–160°C.

Found: N, 11·2%.

$C_{22}H_{15}N_3O_3$ requires: N, 11·4%.

3.20 2-[2-(5-Cyanonaphth[1,2-*d*]oxazolyl)]malondialdehyde (VIII)

This was prepared by the method used for the preparation of **IIb**, starting from **VII**. Yield 60%, m.p. 225–226°C. It was crystallised from ethanol as brown needles. Yield 12 g, m.p. 230–231°C. It gave a violet colouration with ethanolic ferric chloride.

Found: C, 68·0; H, 2·8; N, 10·5%.

$C_{15}H_8N_2O_3$ requires: C, 68·2; H, 3·0; N, 10·5%.

3.21 2-(4-Pyrazolyl)-5-cyanonaphth[1,2-*d*]oxazole (XXIVa)

This was prepared by the method used for **Vb**, starting from **VII** and hydrazine hydrate. Yield 78%, m.p. 288–290°C. It crystallised from methanol as grey needles in almost quantitative yield, m.p. 295–296°C.

Found: C, 69·1; H, 2·9; N, 21·4%.

$C_{15}H_8N_4O$ requires: C, 69·2; H, 3·0; N, 21·5%.

3.22 2-(4(1-Phenylpyrazolyl)-5-cyanonaphth[1,2-*d*]oxazole (XXV)

This was prepared by the method used to prepare **VIb**, starting from **VIII** and phenylhydrazine. Yield 80%, m.p. >360°C (methanol).

Found: C, 74·9; H, 3·6; N, 16·6%.

$C_{21}H_{12}N_4O$ requires: C, 75·0; H, 3·5; N, 16·6%.

3.23 Miscellaneous

The azo dye **X**,[3] the methyl ester of 1-nitro-2-hydroxy-3-naphthoic acid (**XVIII**),[4] and 1-acetamido-4-cyano-2-naphthol (**VII**),[5] were prepared by previously described methods.

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