# SOME 1-SUBSTITUTION DERIVATIVES OF 4-ARYL-2,3-DIHALOGENO-1-NAPHTHOLS*

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Alkylation of derivatives of 4-aryl-1-naphthols (*I*— *V*) by 2,3-epoxypropyl chloride in methanolic sodium hydroxide gave epoxy derivatives *VI*, *VIII*, *IX*, *XI* and *XII*, apart from products of cleavage of the oxirane ring, *VII* and *X*. Analogous alkylation of compounds *I*, *IV* and *V* by 2-(N,N-diethylamino)ethyl chloride hydrochloride in a two-phase medium afforded basic ethers *XIII* to *XV*. The cleavage of the oxirane ring in compound *VI* by the action of primary and secondary amines, piperidine and substituted piperazines led to compounds *XVI*—*XXIV*. Reaction of thionyl chloride with compounds *XXI*, *XXII* and *XXIV* gave chloro derivatives *XXV*—*XXVII*. Exposure of compound *XXII* to 4-methylbenzenesulfonyl chloride produced compound *XXVIII*, retaining the secondary alcoholic group. In an antineoplastic screening *in vivo* none of the compounds prepared had an appreciable activity. Compound *XVII*, being an analogue of propranolol, was used in the test of isoproterenolic tachycardia, and showed a beta-lytic effect comparable with that of propranolol.

In the preceding communications[1-7] we described syntheses of derivatives of 4-aryl--1-naphthols, as model compounds structurally related to lignanes of the podophyllotoxin type. Some of these derivatives exhibited weak antineoplastic effects in *vivo* on experimental transplanted tumours. Besides, certain derivatives of 4-aryl-1-naphthols proved useful intermediates for synthesis of benzo[*c*]fluorene derivatives[6], heterocyclic systems of benzo[*g*]phthalazine and benzo[*f*]isoindoline[8]. The group of benzo[*c*]fluorene derivatives has become a source of pharmacologically active compounds, exhibiting significant antibacterial[9], antiviral[10], interferonogenic[10,11] and antineoplastic effects[12], depending on the nature of the substituents and on the position of their attachment to the benzo[*c*]fluorene skeleton.

As a sequel to our preceding studies on the syntheses and biological activity of derivatives of 4-aryl-1-naphthols, the present paper describes further 1-substitution derivatives of 2,3-disubstituted 4-aryl-1-naphthols *I* — *V* (compounds *VI* — *XXVIII*, Table I) and preliminary results in a screening assay of selected compound for antineoplastic activity.

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TABLE I

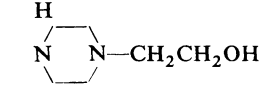
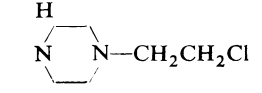
1-Substitution derivatives of 4-aryl-1-naphthols

| Compound X | $R^1$ $R^2$ | Molecular formula (mol.mass) | M.p., °C Solvent | Calculated/Found | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | H C | % H | % N | % Br | % Cl |
| *VI* | H | $C_{19}H_{14}Br_2O_2$ | 124–126 | 52·57 | 3·25 | — | 36·81 | — |
| Br | $CH_2CH(O)CH_2$ | (434·2) | (benzene) | 52·41 | 3·18 | — | 36·54 | — |
| *VII* | H | $C_{19}H_{15}Br_2ClO$ | [b] | 48·49 | 3·21 | — | | |
| Br | $CH_2CH(OH)CH_2Cl$ | (470·6) | | 48·59 | 3·09 | — | | |
| *VIII* | H | $C_{21}H_{14}N_2O_2$ | 173–175 | 77·28 | 4·32 | 8·58 | — | — |
| CN | $CH_2CH(O)CH_2$ | (326·4) | (chloroform) | 77·19 | 4·36 | 8·63 | — | — |
| *IX* | $CH_3$ | $C_{21}H_{18}Br_2O_2$ | Q121–122 | 54·57 | 3·93 | — | 34·58 | — |
| Br | $CH_2CH(O)CH_2$ | (462·2) | (benzene) | 54·77 | 3·91 | — | 34·92 | — |
| *X* | $CH_3$ | $C_{21}H_{19}Br_2ClO$ | 137–139 | 50·58 | 3·84 | — | 32·05 | 7·11 |
| Br | $CH_2CH(OH)CH_2Cl$ | (498·7) | (benzene) | 51·06 | 3·90 | — | 31·80 | 7·13 |
| *XI* | $C_2H_5$ | $C_{23}H_{22}Cl_2O_2$ | 62–64 | 68·83 | 5·53 | — | — | 17·67 |
| Cl | $CH_2CH(O)CH_2$ | (401·3) | (benzene) | 68·72 | 5·57 | — | — | 17·67 |
| *XII* | $C_2H_5$ | $C_{23}H_{22}Br_2O_2$ | 86–87 | 56·35 | 4·52 | — | 32·60 | — |
| Br | $CH_2CH(O)CH_2$ | (490·3) | (benzene) | 56·69 | 4·48 | — | 32·89 | — |
| *XIII*[a] | H | $C_{22}H_{24}Br_2ClNO$ | 215–217 | 51·43 | 4·71 | 2·73 | 31·12 | 6·90 |
| Br | $CH_2CH_2N(C_2H_5)_2$ | (513·8) | (ethanol) | 51·20 | 4·67 | 2·45 | 31·40 | 6·91 |

TABLE I
(*Continued*)

| Compound | $R^1$ | Molecular formula | M.p., °C | Calculated/Found | | | | |
|---|---|---|---|---|---|---|---|---|
| X | $R^2$ | (mol.mass) | Solvent | % C | % H | % N | % Br | % Cl |
| *XIV*[a] | $C_2H_5$ | $C_{26}H_{32}Cl_3NO$ | 176—178 | 64·93 | 6·71 | 2·91 | — | 22·12 |
| Cl | $CH_2CH_2N(C_2H_5)_2$ | (480·9) | (chloroform) | 64·69 | 6·64 | 2·60 | — | 22·38 |
| *XV*[a] | $C_2H_5$ | $C_{26}H_{32}Br_2ClNO$ | 189—192 | 54·80 | 5·66 | 2·46 | | |
| Br | $CH_2CH_2N(C_2H_5)_2$ | (569·8) | (chloroform) | 55·04 | 5·86 | 2·36 | | |
| *XVI* | H | $C_{20}H_{19}Br_2NO_2$ | 125—127 | 51·64 | 4·12 | 3·01 | 34·36 | — |
| OH | $NHCH_3$ | (465·2) | (ethanol) | 51·95 | 3·87 | 2·67 | 34·42 | — |
| *XVII* | H | $C_{22}H_{23}Br_2NO_2$ | 229—232 | 53·56 | 4·70 | 2·84 | 32·40 | — |
| OH | $NHCH(CH_3)_2$ | (493·2) | (ethanol) | 53·47 | 4·60 | 2·69 | 32·60 | — |
| *XVIII* | H | $C_{27}H_{33}Br_2NO_2$ | 70—72 | 57·56 | 5·90 | 2·49 | 28·37 | — |
| OH | $NH(CH_2)_7CH_3$ | (563·4) | (ethanol) | 57·62 | 5·90 | 2·62 | 28·16 | — |
| *XIX* | H | $C_{24}H_{25}Br_2NO_2$ | 108—110 | 55·51 | 4·85 | 2·70 | 30·78 | — |
| OH |  | (519·3) | (tetrachloromethane) | 55·54 | 4·88 | 2·82 | 30·55 | — |
| *XX* | H | $C_{23}H_{25}Br_2NO_2$ | [c] | 54·46 | 4·97 | 2·76 | 31·51 | — |
| OH | $N(C_2H_5)_2$ | (507·3) | | 54·56 | 5·06 | 2·72 | 31·81 | — |
| *XXI* | H | $C_{21}H_{21}Br_2NO_3$ | 118—120 | 50·93 | 4·27 | 2·83 | 32·27 | — |
| OH | $NHCH_2CH_2OH$ | (495·2) | (benzene) | 50·76 | 4·32 | 3·12 | 32·23 | — |
| *XXII* | H | $C_{23}H_{25}Br_2NO_4$ | 138—140 | 51·22 | 4·67 | 2·60 | 29·64 | — |
| OH | $N(CH_2CH_2OH)_2$ | (539·3) | (ethanol) | 51·54 | 4·81 | 2·37 | 29·75 | — |
| *XXIII* | H | $C_{24}H_{26}Br_2N_2O_2$ | 143—145 | 53·95 | 4·96 | 5·24 | 29·91 | — |
| OH |  | (534·3) | (ethanol) | 54·28 | 5·20 | 5·24 | 30·04 | — |

TABLE I
(*Continued*)

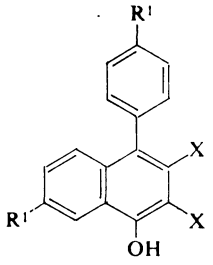
| Compound X | $R^1$ $R^2$ | Molecular formula (mol.mass) | M.p., °C Solvent | Calculated/Found | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | % C | % H | % N | % Br | % Cl |
| *XXIV* | H | $C_{25}H_{28}Br_2N_2O_3$ | 128–129 | 53·21 | 5·00 | 4·96 | 28·32 | — |
| OH |  | (564·4) | (ethanol) | 53·52 | 5·23 | 4·94 | 28·39 | — |
| *XXV* | H | $C_{21}H_{19}Br_2Cl_2N$ | 215–218 | 47·40 | 3·60 | 2·63 | 30·03 | 12·33 |
| Cl | $NHCH_2CH_2Cl$ | (532·1) | (benzene) | 46·99 | 3·93 | 2·46 | 29·72 | 13·23 |
| *XXVI* | H | $C_{23}H_{22}Br_2Cl_3NO$ | 105–110 | 46·46 | 3·73 | 2·36 | 26·88 | 17·89 |
| Cl | $N(CH_2CH_2Cl)_2$ | (594·6) | (benzene) | 46·59 | 3·93 | 2·40 | 26·61 | 17·71 |
| *XXVII* | H | $C_{25}H_{26}Br_2Cl_2N_2O$ | 106–107 | 49·94 | 4·36 | 4·66 | 26·58 | 11·79 |
| Cl |  | (601·3) | (ethanol) | 50·09 | 4·51 | 4·30 | 26·30 | 11·65 |
| *XXVIII* | H | $C_{23}H_{25}Br_2Cl_2NO_2$ | 113–115 | 47·78 | 4·36 | 2·42 | 27·64 | 12·26 |
| OH | $N(CH_2CH_2Cl)_2$ | (578·2) | (benzene) | 48·02 | 4·04 | 2·24 | 27·30 | 12·11 |

[a] Hydrochloride; [b] sirupy product; [c] $n_D^{20}$ 1·6190.

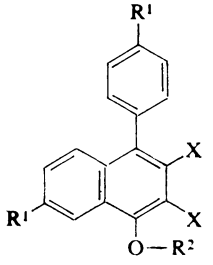
Alkylation of the hydroxy group in the 4-aryl-1-naphthol derivatives *I* – *V* by the action of 2,3-epoxypropyl chloride in methanolic sodium hydroxide at room temperature by the described method[13] in a modified procedure, afforded good yields of the 2,3-epoxy derivatives *VI*, *VIII*, *IX*, *XI* and *XII*. As by-products we obtained small amounts of derivatives of 1-naphthoxy-3-chloro-2-propanol, formed by the action of sodium naphtholates (from the starting products) on 2,3-epoxypropyl chloride, leading to cleavage of its oxirane ring. These by-products were detected in all reaction mixtures (TLC), but in view of their minor contents they were isolated only in the case of the starting compounds *I* and *III*, giving rise to by-products *VII* and *X*.

Alkylation of the hydroxy group of compounds *I*, *IV* and *V* by 2-(N,N-diethylamino)ethyl chloride hydrochloride in a boiling two-phase medium water–toluene, in the presence of sodium hydroxide, afforded basic ethers *XIII* – *XV*, which were characterized in the form of hydrochlorides.

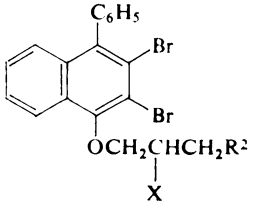
To obtain 1-substitution derivatives of 4-phenyl-2,3-dibromo-1-naphthol, having a propanolamine residue in their molecules (compounds *XVI* – *XXIV*), we made use of the ready celavage of the oxirane ring in compound *VI* for reactions with



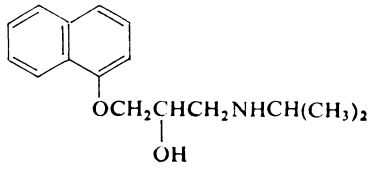

*I*: $R^1$ = H, X = Br (ref.[2])
*II*: $R^1$ = H, X = CN (ref.[3])
*III*: $R^1$ = $CH_3$, X = Br (ref.[2])
*IV*: $R^1$ = $C_2H_5$, X = Cl (ref.[2])
*V*: $R^1$ = $C_2H_5$, X = Br (ref.[1])




*VI* – *XV*




*XVI* – *XXVIII*




*XVIIa*

various primary and secondary amines, piperidine and substituted piperazines. These reactions were carried out either by boiling the compound *VI* with the corresponding amino components in toluene or dioxan (method *A*), or in an autoclave at temperatures 140–150°C (method *B*). The condensate of *VI* with isopropylamine (*XVII*) can be regarded as a derivative of (±)-propranolol (*XVIIa*), which exhibits affinity to the lung tissue. If administered, it gathers in the lungs to a high level[14], the (–) enantiomer being responsible for the beta-adrenergic blockade, whereas the (+) enantiomer is betalytically ineffective. The racemic compounds *XVII* was used as a carrier of alkylating agents with selective cytotoxic effects to the neoplastic tissue. As a contribution to the research of substances with potential specific effects on the lung tissue[15,16], we have prepared compounds having a cytotoxic 2-chloroethylamine or bis(2-chloroethyl)amine residue in the molecule. Conversion of the aliphatic hydroxy compounds *XXI*, *XXII* and *XXIV* into the chloro derivatives *XXV*–*XXVII* was accomplished by the action of thionyl chloride at the boiling temperature, the procedure being a modification of the method described[17].

To convert selectively the primary alcoholic groups in compound *XXII* into the corresponding bis-chloro derivative, without affecting the secondary alcoholic group in the 2-propanol residue (compound *XXVIII*), we used the reaction of compound *XXII* with 4-methylbenzenesulphonyl chloride in dimethylformamide. This reaction was first described by Edington[18] as a side reaction proceeding in tosylation of primary alcohols and was employed later[16] for regioselective chlorination in the preparation of analogous compounds.

Antineoplastic activity of some of the compounds prepared was tested by the usual screening method, with *s.c.* or *p.o.* administration to animals with experimental transplanted tumours[19,20], *viz.* mice with tumours S 180 (the Crocker sarcoma), HK (mammary gland adenocarcinoma), Kr 2 (the Krebs ascitic tumour), Sa 37 (ascitic sarcoma), and rats with the Yoshida ascitic tumour (Y). In these tests the 1-substitution derivatives of 4-aryl-1-naphthols showed only a weak antineoplastic activity. This finding is consistent with our previous results, demonstrating a narrow spectrum of efficacy; as a rule only the tumour size was reduced, or the total ascitokrite. Thus compound *XIII* in a dose of 200 mg/kg *p.o.* reduced the size of tumouss Sa 37 by 38% and produced a statistically significant decrease of the total ascitokrite (20%). A similar effect was observed with compound *XV* in the same dose, but the times of survival were shorter. Compound *XVII* in a subtoxic dose of 100 mg/kg *p.o.* reduced the size of tumours Sa 37 by 44%, with a simultaneous decrease in the total ascitokrite by 41%. However, in a dose of 200 mg/kg *p.o.* it statistically significantly extended the survival of rats with Y tumours by 44%, in half the dose by 30%. Compound *XXIV* in a dose of 200 mg/kg *p.o.* reduced the size of tumours Sa 37 by 33% and the values of the total ascitokrite by 26%, in mice with tumours S 180 it extended the survival by 38%. However, compound *XXVI*, having a bis(2-chloroethyl)amino residue in the molecule, has failed to show even

a trace of antineoplastic activity, which does not substantiate our ideas on the struture of an active cytotoxic compound, but is not at variance with the biologic activity of analogous compounds[16].

In testing the efficacy of compound *XXVII* on cells of the Yoshida tumours (by following the incorporation of $^{14}C$ into fractions of cells insoluble in dilute trichloroacetic acid during a short-term cultivation *in vitro* using a mixture of L-[U-$^{14}C$]amino acids as precursor, and by the method described in refs[21-24], the value of $IC_{50}$ (measure of cytotocixity) was higher than $10^{-4}$ mol $l^{-1}$, which demonstrates a weak effect of the compound on the proteosynthesis of the tumour cells, and a low cytotoxicity. Consequently, any antineoplastic effect of the compound *in vivo* is very improbable. This conclusion is consistent with the results of tests on animals with the tumour L 1210, in which the compound *XXVII* administered *i.p.* in doses of 25 – 350 mg/kg showed no effect.

## EXPERIMENTAL

The melting points were determined on the Kofler stage and are not corrected. The samples for elemental analyses were dried over phosphorus pentoxide at a pressure of 70 Pa and temperatures proportional to the melting points. The individuality of the samples and composition of the reaction mixtures were examined by TLC on reflex foils Silufol $UV_{254}$ (Kavalier); the spots were detected by quenching UV light at 254 nm. The $^1H$ NMR spectra were recorded with a spectrometer Tesla BS 487 C, employing 10% solutions in deuteriochloroform or hexadeuteriodimethyl sulphoxide with tetramethylsilane as internal standard. The IR spectra were measured in an apparatus Infrascan (Hilger) with 5% solutions in chloroform or by the KBr technique. The mass spectra were measured in an apparatus MS-9.

### Condensation of 4-Aryl-1-naphthol Derivatives with 2,3-Epoxypropyl Chloride (Compounds *VI*—*XII*)

To a stirred methanolic solution of sodium hydroxide was added, at 20—25°C, a derivative of a 4-aryl-1-naphthol (*I*— *V*), then an excess of 2,3-epoxypropyl chloride was added in one portion. The stirring was continued for 2— 5 days, any contact of the mixture with aerial moisture and carbon dioxide being excluded.The separated solid was collected on a filter, washed with water and dried (portion 1). The filtrate was taken to dryness.The residue was dissolved in benzene or a mixture of benzene with 20% of chloroform, washed with 2% aqueous sodium hydroxide and water, dried with anhydrous magnesium sulphate and concentrated to crystallize (portion 2). The combined portions 1 and 2 were recrystallized. The minor products (*VII*, *X*) were obtained from concentrated mother liquors after crystallization of *VI* and/or *IX* by column chromatography on alumina.

*VI*: 4-Phenyl-2,3-dibromo-1-naphthol (*I*) (164·4 g, 0·435 mol), sodium hydroxide (20 g, 0·5 mol), methanol (400 ml), reaction time 48 h, 2,3-epoxypropyl chloride (339 ml, 4·35 mol), yield 162 g (85%). $^1H$ NMR spectrum (deuteriochloroform): $\delta$ 8·20 (bd, 1 H, $J$ = 8·0 Hz, $C_{(8)}$—H), 7·10—7·70 (m, 8 H, Ar—H), 4·42, 4·02 (dd, 2 H, $J$ = 11·0; 6·0; 3·0 Hz, $ArOCH_2$), 3·52 (m, 1 H, OCH (cycl.)), 3·85 (m, 2 H, $OCH_2$ (cycl.)). *VII*: Column chromatography ($Al_2O_3$, benzene) gave 1·5 g (0·7%) of *VII*. $^1H$ NMR spectrum (deuteriochloroform): $\delta$ 8·15 (bd, 1 H,

$C_{(8)}$—H), 7·10—7·60 (m, 8 H, Ar—H), 4·30 (m, 3 H, $OCH_2CHO$—), 3·92 (d, 2 H, $J$ = 5·0 Hz, $CH_2Cl$), 2·78 (bs, 1 H, OH). Mass spectrum: $m/z$ = 470 ($M^+$ corresponds to $C_{19}H_{15}Br_2ClO_2$).

*VIII*: 4-Phenyl-2,3-dicyano-1-naphthol (*II*) (2·7 g, 10 mmol), sodium hydroxide (0·46 g, 11·5 mmol), methanol (20 ml), 2,3-epoxypropyl chloride (9·3 g, 0·1 mol), reaction time 5 days, yield 2·2 g (67%). $^1$H NMR spectrum (deuteriochloroform): $\delta$ 8·45 (bd, 1 H, $C_{(8)}$—H), 7·20 to 7·90 (m, 8 H, Ar—H), 4·90, 4·35 (dd, 2 H, $J$ = 11·0; 6·0; 3·0 Hz, $ArOCH_2$), 3·65 (m, 1 H, OCH (cycl..)) 2·90 (m, 2 H, $OCH_2$ (cycl.). IR spectrum (chloroform): 2 240 (CN), 1 610, 1 580 $cm^{-1}$ (Ar).

*IX*: 7-Methyl-4-(4-methylphenyl)-2,3-dibromo-1-naphthol (*III*) (3·98 g, 10 mmol), sodium hydroxide (0·8 g, 20 mmol), methanol (20 ml), 2,3-epoxypropyl chloride (9·3 g, 0·1 mol), reaction time 3 days, yield 2·6 g (56·3%). $^1$H NMR spectrum (deuteriochloroform): $\delta$ 7·98 (bs, 1 H, $C_{(8)}$—H), 7·00—7·40 (m, 6 H, Ar—H), 4·42, 4·09 (dd, 2 H, $J$ = 11·0; 6·0; 3·0 Hz, $ArOCH_2$), 3·59 (m, 1 H, OCH (cycl.)), 2·90 (m, 2 H, $OCH_2$ (cycl.)), 2·50 (s, 3 H, $ArCH_3$), 2·45 (s, 3 H, $ArCH_3$). *X*: Column chromatography ($Al_2O_3$, benzene) gave 0·3 g (6%). $^1$H NMR spectrum (deuteriochloroform): $\delta$ 7·88 (bs, 1 H, $C_{(8)}$—H), 6·90—7·40 (m, 6 H, Ar—H), 4·35 (m, 3 H, $OCH_2CHO$—), 3·82 (d, 2 H, $J$ = 5·0 Hz, $CH_2Cl$), 2·99 (bd, 1 H, $J$ = 6·0 Hz, OH), 2·48 (s, 3 H, $ArCH_3$), 2·45 (s, 3 H, $ArCH_3$).

*XI*: 7-Ethyl-4-(4-ethylphenyl)-2,3-dichloro-1-naphthol (*IV*) (3·45 g, 10 mmol), sodium hydroxide (0·8 g, 20 mmol), methanol (20 ml), 2,3-epoxypropyl chloride (9·3 g, 0·1 mol), reaction time 4 days, yield 2·6 g (64·8%), $^1$H NMR spectrum (deuteriochloroform): $\delta$ 8·00 (bs, 1 H, $C_{(8)}$—H), 7·25 (bs, 2 H, $C_{(6)}$—H, $C_{(5)}$—H), 7·30 (d, 2 H, $J$ = 9·0 Hz, 4-substitutted Ar), 7·12 (d, 2 H, $J$ = 9·0 Hz, 4-substituted Ar), 4·43, 4·07 (dd, 2 H, $J$ = 11·0; 6·0; 3·0 Hz, $ArOCH_2$), 3·52 (m, 1 H, OCH (cycl.)), 2·50—3·00 (m, 6 H, $OCH_2$ (cycl.), 2 $ArCH_2$—), 1·32 (t, 3 H, $J$ = 7·0 Hz, $ArCH_2$—$CH_3$), 1·30 (t, 3 H, $J$ = 7·0 Hz, $ArCH_2$—$CH_3$).

*XII*: 7-Ethyl-4-(4-ethylphenyl)-2,3-dibromo-1-naphthol (*V*) (4·34 g, 10 mmol), sodium hydroxide (0·8 g, 20 mmol), methanol (20 ml), 2,3-epoxypropyl chloride (9·3 g, 0·1 mol), reaction time 3 days, yield 2·3 g (46·9%). $^1$H NMR spectrum (deuteriuchloroform): $\delta$ 8·00 (bs, 1 H, $C_{(8)}$—H), 7·25 (bs, 2 H, $C_{(6)}$—H, $C_{(5)}$—H), 7·30 (d, 2 H, $J$ = 9·0 Hz, 4-substituted Ar), 7·10 (d, 2 H, $J$ = 9·0 Hz, 4-substituted Ar), 4·45, 4·08 (dd, 2 H, $J$ = 11·0; 6·0; 3·0 Hz, $ArOCH_2$), 3·59 (m, 1 H, OCH (cycl.)), 2·50—3·00 (m, 6 H, $OCH_2$ (cycl.), 2 $ArCH_2$—), 1·34 (t, 3 H, $J$ = 7·0 Hz, $ArCH_2$—$CH_3$), 1·31 (t, 3 H, $J$ = 7·0 Hz, $ArCH_2$—$CH_3$).

4-Aryl-2,3-dihalogeno-1-(2-(N,N-diethylamino)ethoxy)naphthalene Hydrochlorides (*XIII—XV*)

To a stirred mixture of toluene and aqueous potassium hydroxide was added a 4-aryl-2,3-dihalogeno-1-naphthol (*I, IV, V*) and allowed to dissolve, then 2-(N,N-diethylamino)ethyl chloride hydrochloride (2·5 equivalents) was added. The mixture was boiled under a reflux condenser for 6 to 8 h under stirring, then allowed to stand overnight. The aqueous layer was discarded and the toluene layer was washed with approx. a half volume of 20% aqueous potassium hydroxide, twice with a saturated solution of sodium chloride, dried with anhydrous sodium sulphate and taken to dryness. The residue was dissolved in ethanol, acidified with an ethanolic solution of hydrogen chloride (to pH *c.*3) and concentrated to crystallize.

*XIII*: Naphthol *I* (7·6 g, 20 mmol), potassium hydroxide (6·6 g, 0·12 mol), 2-(N,N-diethylamino)ethyl chloride hydrochloride (8·5 g, 50 mmol), water (40 ml), toluene (90 ml), reflux for 6 h, yield 9·4 g (91·6%). $^1$H NMR spectrum (deuteriochloroform): $\delta$ 12·69 (bs, 1 H, $NH^+$), 8·15 (bd, 1 H, $J$ = 8·0 Hz, $C_{(8)}$—H), 7·10—7·70 (m, 8 H, ArH), 4·68 (bt, 2 H, $J$ = 4·0 Hz,

$ArOCH_2$), 3·70 (bm, 2 H, after $^2H_2O$ t, $J$ = 4·0 Hz, $N^{(+)}CH_2$), 3·50 (bm, 4 H, after $^2H_2O$ q, $J$ = 7·0 Hz, 2 $N^{(+)}CH_2$), 1·58 (t, 6 H, $J$ = 7·0 H, 2 $N^{(+)}CH_2$—$CH_3$). IR spectrum (chloroform): 1 600, 1 550 (Ar), 2 340, 2 540 $cm^{-1}$ ($N^+H$).

*XIV*: Naphthol *IV* (6·9 g, 20 mmol), 2-(N,N-diethylamino)ethyl chloride hydrochloride (8·5 g, 50 mmol), potassium hydroxide (6·6 g, 0·12 mol), water (40 ml), toluene (100 ml), reflux 8 h, yield 9·0 g (93·7%). $^1H$ NMR spectrum (deuteriochloroform): $\delta$ 12·40 (bs, 1 H, $N^+H$), 7·88 (bs, 1 H, $C_{(8)}$—H), 7·00—7·50 (m, 6 H, ArH), 4·68 (bm, 2 H, after $^2H_2O$ t, $J$ = 4·0 Hz, $ArOCH_2$), 3·78 (bm, 2 H, after $^2H_2O$ t, $J$ = 4·0 Hz, $N^{(+)}CH_2$), 3·52 (bm, 4 H, after $^2H_2O$ q, $J$ = 7·0 Hz, 2 $N^{(+)}CH_2$), 2·88 (q, 2 H, $J$ = 7·0 Hz, $ArCH_2$), 2·78 (q, 2 H, $J$ = 7·0 Hz, $ArCH_2$), 1·58 (bm, 6 H, after $^2H_2O$ t, $J$ = 7·0 Hz, 2 $N^{(+)}CH_2CH_3$, 1·32 t, 6 H, 2 $ArCH_2$—$CH_3$). IR spectrum (chloroform): 1 620, 1 560 (Ar), 2 340, 2 550 $cm^{-1}$ ($N^+H$).

*XV*: Naphthol *V* (4·34 g, 10 mmol), 2-(N,N-diethylamino)ethyl chloride hydrochloride (4·3 g, 25 mmol), potassium hydroxide (3·3 g, 60 mmol), water (20 ml), toluene (50 ml), reflux 8 h, yield 4·3 g (75·4%). $^1H$ NMR spectrum (deuteriochloroform): $\delta$ 12·75 (bs, 1 H, $N^+H$), 7·85 (bs, 1 H, $C_{(8)}$—H), 7·00—7·40 (m, 6 H, ArH), 4·60 (bt, 2 H, $J$ = 4·0 Hz, $ArOCH_2$), 3·75 (bt, 2 H, $J$ = 4·0 Hz, $N^{(+)}CH_2$), 3·48 (bq, 4 H, $J$ = 7·0 Hz, 2 $N^{(+)}CH_2$—), 2·85 (q, 2 H, $J$ = 7·0 Hz, $ArCH_2$—), 2·75 (q, 2 H, $J$ = 7·0 Hz, $ArCH_2$—), 1·51 (t, 6 H, $J$ = 7·0 Hz, 2 $N^{(+)}CH_2$—$CH_3$), 1·31 (t, 6 H, $J$ = 7·0 Hz, 2 $ArCH_2$—$CH_3$). IR spectrum (chloroform): 1 620, 1 560 (Ar), 2 400, 2 550 $cm^{-1}$ ($N^+H$).

Reactions of 4-Phenyl-2,3-dibromo-1-(2,3-epoxypropoxy)naphthalene (*VI*) with Amino Compounds (Compounds *XVI*—*XXIV*)

To a suspension of *VI* in toluene or dioxan was added an excess of the corresponding amino compound and the mixture was refluxed (method *A*), or, with the low-boiling amines, it was heated in a steel autoclave to 140—160°C (method *B*). After the reaction had finished (tests by TLC) the volatile components were distilled off and the residue was purified by crystallization of column chromatography. After the reactions of *VI* with ethanolamine (*XXI*), diethanolamine (*XXII*) and N-(2-hydroxyethyl) piperazine (*XXIV*) toluene was distilled off and the separated solid was collected on a filter and purified by crystallization.

*XVI*: Method *B*, compound *VI* (0·87 g, 2 mmol), toluene (3 ml), methylamine (0·93 g, 30 mmol), heated 7 h to 160°C. Yield 0·45 g (48·4%). $^1H$ NMR spectrum (deuteriochloroform): $\delta$ 8·21 (bd, 1 H, $J$ = 8·0 Hz, $C_{(8)}$—H), 7·00—7·60 (m, 8 H, ArH), 4·15 (m, 3 H, $OCH_2CHO$), 3·20 (bs, 2 H, NH, OH), 2·90 (d, 2 H, $J$ = 5·5 Hz, $NCH_2$), 2·52 (s, 3 H, $NCH_3$).

*XVII*: Method *A*, *VI* (0·43 g, 1 mmol), dioxan (10 ml), isopropylamine (0·6 g, 10 mmol), reflux 28 h. The crude product was purified by column chromatography, the eluant was chloroform; yield 0·2 g (40·8%). Method *VI* (32·5 g, 75 mmol), toluene (70 ml), isopropylamine (22·5 g, 0·37 mol), reaction time 6 h at 160°C. The crude product after being filtered with activated carbon (0·5 g), was purified by crystallization; yield 24·5 g (66·2%). $^1H$ NMR spectrum (hexadeuteriodimethyl sulphoxide): $\delta$ 9·10 (bs, 1 H, NH), 8·40 (bs, 1 H, $J$ = 8·0 Hz, $C_{(8)}$—H), 7·10 to 7·80 (m, 8 H, ArH), 6·22 (bs, 1 H, OH), 4·52 (bm, 1 H, CHO), 4·15 (d, 2 H, $J$ = 6·0 Hz, $ArOCH_2$), 3·35 (m, 4 H, $CH_2NCH_2$), 1·36 (d, 6 H, $J$ = 6·5 Hz, 2 CH—$CH_3$). IR spectrum (KBr): 1 600, 1 575, 1 550 (Ar), 3 360 $cm^{-1}$ (OH, NH).

*XVIII*: Method *B*, *VI* (0·87 g, 2 mmol), toluene (3 ml), n-octylamine (1·3 g, 10 mmol), heated 7 h to 160°C; yield 0·6 g (53·6%). $^1H$ NMR spectrum (deuteriochloroform): $\delta$ 8·21 (bd, 1 H, $J$ = 8·0 Hz, $C_{(8)}$—H), 7·00—7·60 (m, 8 H, ArH), 4·15 (m, 3 H, $OCH_2CHO$), 2·95 (d, 2 H,

$J$ = 5·5 Hz, $NCH_2$), 2·68 (bt, 2 H, $NCH_2$), 2·70 (bs, 2 H, NH, OH), 1·35 (bs, 12 H, $(CH_2)_6$), 0·89 (def. t, 3 H, aliph. $CH_3$).

*XIX*: Method *A*, *VI* (2·2 g, 5 mmol), toluene (5 ml), piperidine (4·3 g, 50 mmol), reflux 8 h, yield 1·6 g (61·7%). $^1$H NMR spectrum (deuteriochloroform): $\delta$ 8·35 (bd, 1 H, $J$ = 8·0 Hz, $C_{(8)}$—H), 7·10—7·70 (m, 8 H, ArH), 4·20 (m, 3 H, $OCH_2CHO$), 3·98 (bs, 1 H, OH), 2·30 to 2·90 (m, 6 H, 3 $NCH_2$), 1·60 (m, 6 H, 3 $CH_2$ (cycl.)). IR spectrum (chloroform): 1 560 (Ar), 3 200 $cm^{-1}$ (OH).

*XX*: Method *B*, *VI* (0·87 g, 2 mmol), toluene (3 ml), diethylamine (0·73 g, 10 mmol), heated 5 h to 160°C. Column chromatography ($Al_2O_3$, benzene) gave 0·68 g (67%) of a sirupy residue; $n_D^{20}$ = 1·619. $^1$H NMR spectrum (deuteriochloroform): 8·36 (bd, 1 H, $J$ = 8·0 Hz, $C_{(8)}$—H), 7·10—7·70 (m, 8 H, ArH), 4·20 (m, 3 H, $OCH_2CHO$), 4·00 (bs, 1 H, OH), 2·50—3·00 (m, 6 H, 3 $NCH_2$), 1·12 (t, 6 H, $J$ = 7·0 Hz, 2 $CH_2$—$CH_3$).

*XXI*: Method *A*, *VI* (17·4 g, 40 mmol), toluene (60 ml), 2-hydroxyethylamine (20 ml), reflux 6 h, yield 16 g (80·8%). $^1$H NMR spectrum (deuteriochloroform, 60°C): $\delta$ 8·20 (bd, 1 H, $J$ = 8·0 Hz, $C_{(8)}$—H), 7·00—7·80 (m, 8 H, ArH), 4·30 (m, 3 H, $OCH_2CHO$), 3·60 (bs, 2 H, 2 OH), 3·75 (bm, 2 H, $CH_2$—OH), 3·00 (bm, 4 H, 2 $NCH_2$).

*XXII*: Method *A*, *VI* (37·7 g, 87 mmol), toluene (130 ml), bis(2-hydroxyethyl)amine (40 ml), reflux 6 h, yield 36·1 g (72·3%). $^1$H NMR spectrum (deuteriochloroform, 60°C): $\delta$ 8·20 (bd, 1 H, $J$ = 8·0 Hz, $C_{(8)}$—H), 7·00—7·60 (m, 8 H, ArH), 4·35 (m, 3 H, $OCH_2CHO$), 4·10 (bs, 1 H, OH), 3·70 (bm, 4 H, 2 $CH_2$—OH), 2·80 (bm, 6 H, 3 $NCH_2$).

*XXIII*: Method *A*, *VI* (0·87 g, 2 mmol), toluene (3 ml), N-methylpiperazine (1 g, 10 mmol), reflux 7 h, yield 0·5 g (47·2%). $^1$H NMR spectrum (deuteriochloroform): $\delta$ 8·30 (bd, 1 H, $J$ = = 8·0 Hz, $C_{(8)}$—H), 7·00—7·60 (m, 8 H, ArH), 4·20 (m, 3 H, $OCH_2CHO$), 3·80 (bs, 1 H, OH), 2·60 (bm, 10 H, 5 $NCH_2$), 2·25 (s, 3 H, $NCH_3$).

*XXIV*: Method *A*, *VI* (17·4 g, 40 mmol), toluene (60 ml), N-(2-hydroxyethyl)piperazine (13 g, 0·1 mol), reflux 8 h, yield 20·7 g (92%). $^1$H NMR spectrum (deuteriochloroform): $\delta$ 8·25 (bd, 1 H, $J$ = 8·0 Hz, $C_{(8)}$—H), 7·00—7·70 (m, 8 H, ArH), 4·20 (m, 3 H, $OCH_2CHO$), 3·60 (bt, 2 H, $J$ = 5·5 Hz, $CH_2$—OH), *c.* 3·00 (bs, 2 H, 2 OH), *c.* 2·60 (bm, 12 H, 6 $NCH_2$).

1-(4-Phenyl-2,3-dibromo-1-naphthyloxy)-2-chloro-3-(2-chlorethylamino)propane (*XXV*)

Excluding aerial moisture, a solution of *XXI* (9·9 g, 20 mmol) in thionyl chloride (40 ml) was boiled under a reflux condenser for 10 h.The remaining thionyl chloride was distilled off *in vacuo* (water jet pump) and the residue was distributed between 100 ml portions of chloroform and 2M--NaOH. The chloroform layer was twice washed with water, dried with anhydrous sodium sulphate and concentrated to crystallize; yield 4·9 g (46%) of *XXV*. $^1$H NMR spectrum (hexadeuteriodimethyl sulphoxide, 90°C)0 $\delta$ 8·40 (bd, 1 H, $J$ = 8·0 Hz, $C_{(8)}$—H), 7·10—7·80 (m, 8 H, ArH), 4·60 (m, 1 H, CHCl), 4·25 (d, 2 H, $J$ = 5·0 Hz, $ArOCH_2$), 4·10 (t, 2 H, $J$ = 6·5 Hz, $CH_2Cl$), 3·51 (t, 2 H, $J$ = 6·5 Hz, $NCH_2$), 3·40 (m, 2 H, $NCH_2$).

1-(4-Phenyl-2,3-dibromo-1-naphthyloxy)-2-chloro-3-(bis(2-chloroethyl)amino)propane (*XXVI*)

Ecluding aerial moisture, a solution of *XXII* (36·1 g, 0·067 mol) in thionyl chloride (70 ml) was boiled under a reflux condenser for 3 h. The remaining thionyl chloride was distilled off *in vacuo*; the residue was taken into water and neutralized with concd. ammonium hydroxide to pH 8. The separated solid was collected on a filter, washed with water and dried. Crystallization from ethanol gave 15·1 g (37·9%) of *XXVI*. $^1$H NMR spectrum (hexadeuteriodimethyl

sulphoxide, 90°C): $\delta$ 8·30 (bd, 1 H, $J$ = 8·0 Hz, $C_{(8)}$—H), 7·00—7·70 (m, 8 H, ArH), 4·60 (m, 3 H, $OCH_2CHCl$), 3·70 (t, 4 H, $J$ = 7·0 Hz, 2 $CH_2Cl$), 3·30 (m, 2 H, $NCH_2$), 3·12 (t, 4 H, $J$ = 7·0 Hz, 2 $NCH_2$).

1-(4-Phenyl-2,3-dibromo-1-naphthyloxy)-2-chloro-3-(4-(2-chloroethyl)piperazine-1-yl)propane (*XXVII*)

A suspension of *XXIV* (5·6 g, 10 mmol) in thionyl chloride (15 ml) was boiled under a reflux condenser for 8 h, then allowed to stand overnight at room temperature. After the removal of thionyl chloride by distillation, the residue was dissolved in water (50 ml) and the solution was alkalinized with solid sodium carbonate. The separated crude product was collected on a filter, washed with water and dried (6·5 g); then it was dissolved in a boiling mixture of benzene and ethanol (180 ml), filtered with activated carbon and concentrated to crystallize; yield 3·2 g (53%) of *XXVII*. $^1$H NMR spectrum (deuteriochloroform): $\delta$ 8·30 (bd, 1 H, $J$ = 8·0 Hz, $C_{(8)}$—H), 7·00—7·60 (m, 8 H, ArH), 4·40 (m, 3 H, $OCH_2CHO$), 3·55 (t, 2 H, $J$ = 7·0 Hz, $CH_2Cl$), *c.* 2·85 (m, 4 H, 2 $NCH_2$), 2·60 (bs, 3 H, 4 $NCH_2$ (cycl.)).

1-(4-Phenyl-2,3-dibromo-1-naphthyloxy)-3-(bis(2-chloroethyl)amino)-2-propanol (*XXVIII*)

To a solution of *XXII* (5·4 g, 10 mmol) in dimethylformamide (30 ml) was added 4-methylbenzenesulphonyl chloride (4·0 g, 21 mmol) and the mixture was stirred at 55—60°C for 2 h, after which time no presence of the starting compound could be detected by TLC. After concentration in a vacuum evaporator the residue was dissolved in benzene (50 ml). The solution was washed with 1M-NaOH (50 ml) and water, dried with anhydrous sodium sulphate and distilled. The residue (6·0 g) was an oil, composed of the product and two other compounds. Column chromatography on silica gel (with chloroform as eluant) and crystallization gave 3·0 g (52%) of *XXVIII*. $^1$H NMR spectrum (deuteriochloroform): $\delta$ 8·30 (bd, 1 H, $J$ = 8·0 Hz, $C_{(8)}$—H), 7·10—7·70 (m, 8 H, ArH), 4·20 (m, 3 H, $OCH_2CHO$), 3·62 (t, 4 H, $J$ = 7·0 Hz, 2 $CH_2Cl$), 3·40 (bs, 1 H, OH), 3·30 (t, 4 H, $J$ = 7·0 Hz, 2 $NCH_2$), 2·96 (d, 2 H, $J$ = 6·0 Hz, $NCH_2$).

*The elemental analyses were performed by Mrs J. Komancová (Analytical Department, head: Dr J. Körbl). The* $^1$H NMR *spectra were measured and interpreted by Dr J. Holubek (Physicochemical Department, head: Dr B. Kakáč).*

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