129. Design and Synthesis of 5-Lipoxygenase Inhibitors

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Based on the substrate specificity for 5-lipoxygenase and cyclooxygenase and the known stereochemical course of the reaction, a hypothetical model of the enzyme active site was developed and used to design 2 types of selective inhibitors of 5-lipoxygenase. Both inhibitor types used aromatic rings in place of (*Z*)-olefins of the substrate and were designed to mimic the nonpolar end of arachidonic acid. One inhibitor type used a carboxylic-acid interaction with the O-binding centre of the enzyme in analogy with known cyclooxygenase inhibitors, whereas a second type employed a hydroxylamine function to interact with a presumed tyrosine or cysteinyl radical predicted to be in the enzyme active site. Selective 5-lipoxygenase inhibitors were 7-(hexyloxy)naphthalene-2-acetic acid (**1**) and *N*-methyl-*N*-(7-propoxynaphthalene-2-ethyl)hydroxylamine (**2**). Structure-activity relationships for both types of inhibitors are discussed.

Introduction. – Arachidonic-acid metabolites have important regulatory functions in a variety of cell types [1–6]. In mammalian cells, there are two main oxidative pathways which lead to biologically active products. Firstly, *via* cyclooxygenase and a cascade of subsequent reactions, the prostaglandins, thromboxanes, and prostacyclin are produced. Secondly, there is the lipoxygenase pathway where a series of related enzymes add a hydroperoxide group to positions 5, 8, 9, 11, 12, and 15 of arachidonic acid, whereby the enzyme which introduces the hydroperoxide at the 5 position leading to the formation of the leukotrienes is of particular importance (see *Scheme 1*) [3–8].

Of the arachidonic-acid metabolites, leukotriene B_4 (LTB_4) was of special interest to us as it has been reported to be strongly chemotactic for polymorphonuclear leukocytes [9] and had been suggested to be implicated in the pathogenesis of inflammation, asthma, and psoriasis [5] [10]. *In-vitro* experiments have demonstrated that the release of LTB_4 from activated phagocytic cells can be blocked by the action of corticosteroids which indirectly inhibit phospholipase A_2, the enzyme which releases arachidonic acid from phospholipids [11]. Corticosteroids have other actions apart from inhibition of LTB_4 release which result in serious side effects [12]. In addition, they inhibit the formation of prostaglandins causing gastric ulceration and constipation as is known for the cyclooxygenase-inhibiting non-steroidal antiinflammatory drugs of the aspirin type. The design of selective 5-lipoxygenase inhibitors as potential antiinflammatory and antipsoriatic agents which did not affect cyclooxygenase and, thereby, avoid the above side effects appeared a worthwhile goal [3] [13] [14].

At the start of this work, there was no detailed structural information available on any of the lipoxygenases. Only recently, amino acid sequence data for some lipoxygenases

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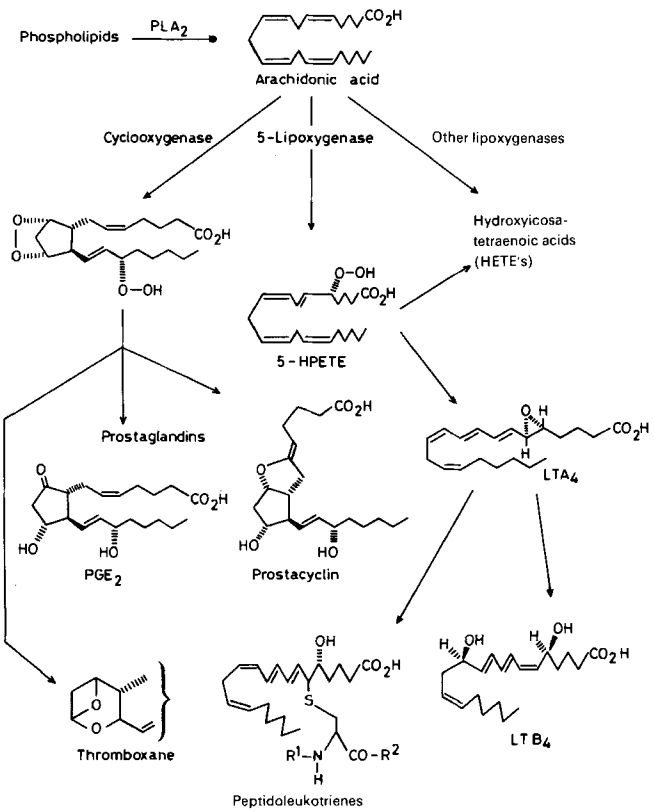
Scheme 1. *Pathways for the Metabolism of Arachidonic Acid*



have become available [15–18]. However, from the information reported on enzymes which oxidize arachidonic acid, the following characteristics appeared important:

1) Lipoxygenases only catalyse the oxidation of unsaturated fatty acids which contain (*Z,Z*)-1,4-diene systems. They stereospecifically remove one H-atom (H_{si} from C(7) of arachidonic acid in the case of 5-lipoxygenase), presumably as a H-radical, from the 3-methylidene group and cause the migration of one double bond to form a (*Z,E*)-1,3-diene [19].

2) The removal of the H-atom and addition of O_2 occur on opposite faces of the substrate molecule.

3) In cases where detailed substrate structural studies have been carried out, the lipoxygenase (or cyclooxygenase) has been particularly sensitive to variations in the length of the alkyl group attached to the diene to be oxidized (*i.e.* the non-polar end), whereas increasing or decreasing the length of the carboxyl end of the chain was tolerated. This suggests that the non-polar end of the substrate is the major unit for recognition by the enzyme [20–23].

4) Soybean lipoxygenase contains 1 mol of non-haem Fe per mol of enzyme. In the resting form, the Fe is in the Fe(II) state and changes to the Fe(III) state on activation [24–29].

5) The 5-lipoxygenase has recently been purified from human leukocytes [30]. It requires Ca^{++} and ATP and consists of a membrane-bound component and two cytosolic units.

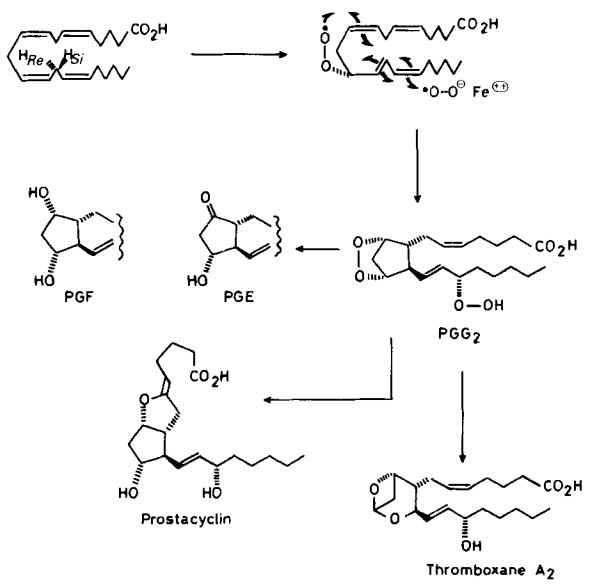
6) The purified 5-lipoxygenase also catalyses the converison of the 5-(hydroperoxy)icosatetraenoic acid to leukotriene A_4 [31].

7) The K_M of arachidonic acid as a substrate for 5-lipoxygenase is 12.2 ± 4.5 μM [32].

A large number of inhibitors are known for cyclooxygenase, and as the first addition of O_2 to arachidonic acid by this enzyme is mechanistically similar to that of lipoxygenases, we attempted to adapt the wealth of information available on structure-activity relationships for cyclooxygenase to lipoxygenase.

Cyclooxygenase adds 2 molecules of O_2 to arachidonic acid. The first and rate-determining step is the removal of H_{Si} at C(13) and introduction of a hydroperoxyl radical at C(11) in a manner analogous to that of lipoxygenases [33]. The formed intermediate remains enzyme-bound and reacts with a second molecule of O_2 at C(15) with allylic rearrangement and cyclisation to form the endoperoxide PGG_2 which is the precursor of all prostaglandins and thromboxanes (see *Scheme 2*).

Scheme 2. *The Formation of Prostaglandins by Cyclooxygenase*



Cyclooxygenase has a strong preference for substrates having a C_5-alkyl or -alkenyl substituent on the (*Z*,*Z*)-1,4-diene. Analogous unsaturated fatty acids containing chains with 4 or 6 C-atoms in this position are far poorer substrates indicating that the enzyme contains a specific lipophilic pocket enabling it to recognize the appropriate (*Z*,*Z*)-1,4-dienes to be oxidized [34]. By contrast, the specificity of the enzyme for the carboxyl end of the chain appears less critical, and substrates with one less or up to two additional CH_2 groups are accepted [34] [35]. With this in mind, a model of the enzyme responsable for the first addition of O_2 by cyclooxygenase was developed (see *Fig. 1*).

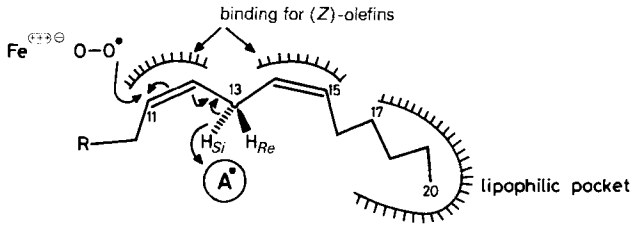


Fig. 1. *Model of the active site of cyclooxygenase involved in the first addition of O_2 to arachidonic acid*

A radical centre A•, presumably a cysteine or tyrosine radical, was postulated as the H-radical-abstracting moiety, and in the neighbourhood of C(11) of the substrate, radical-stabilising and O_2-binding (Fe^{3+}) groups were placed. Evidence for the abstraction of a H-atom rather than H^--anion or a proton as the initiating step has recently been provided by the finding that 10,10-difluoroarachidonic acid is also a substrate. The formation of a carbanion or carbonium ion adjacent to a CF_2 group is unlikely considering the observed outcome of the reaction [36]. As inhibitors, we, as have others [37], considered that a carboxylic acid may bind strongly in place of the superoxide anion, or it could bind to a radical-stabilizing group. This interaction combined with the structural requirements for the nonpolar end of substrates led to the hypothesis that carboxylic acids may act as inhibitors if the other structural requirements were fulfilled ((*Z*)-diene and steric requirements for the lipophilic pocket). As a basic structural unit for inhibitors, a (*Z*)-4-decenoic acid with additional π electrons at C(3) was formulated, the π electrons at C(3) serving to make the inhibitor more like the transition state since enzymes bind transition states more tightly than either substrates or products. As circumstantial evidence supporting the hypothesis, the (*Z*)-4-decenoic-acid unit can be found in many known cyclooxygenase inhibitors *(Fig. 2)* [38], and structure-activity relationships such as extending or shortening the chain length led to reduced activity as predicted.

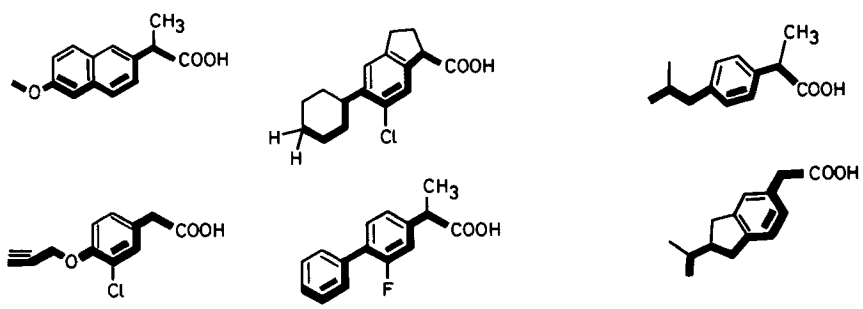


Fig. 2. *Structure comparison of some cyclooxygenase inhibitors*

In a similar way, the 15-lipoxygenase from soybeans also requires a specific alkyl chain attached to the diene to be oxidised and, if the generalisation holds for the 5-lipoxygenase involved in leukotriene synthesis, we would predict that the enzyme contains a large lipophilic pocket which specifically recognises C(9) to C(20) of arachidonic acid in its energetically most stable conformation. Based on this hypothesis, the enzyme model in *Fig. 3* was constructed, and, in analogy with cyclooxygenase, inhibitors

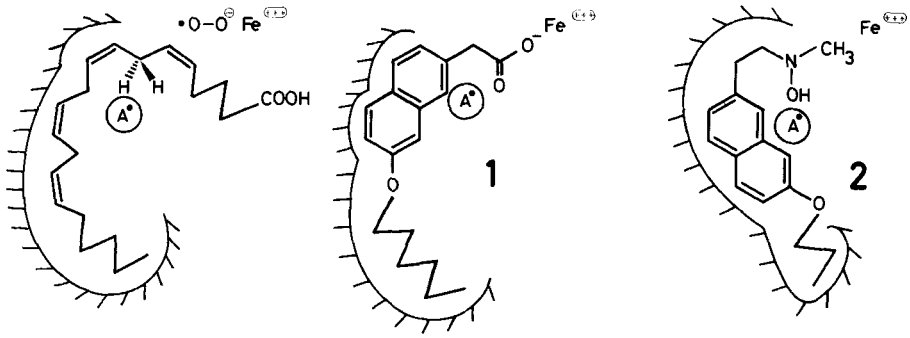


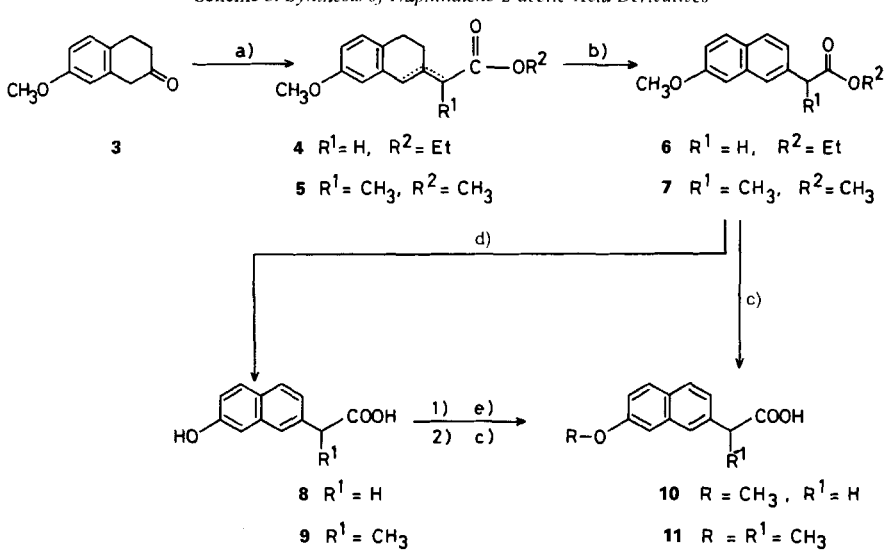
Fig. 3. *Hypothetical model of the active site of 5-lipoxygenase*

related to **1** were prepared. The work described below presents structure-activity relationships for inhibitors of the type **1** and extends the inhibitor design to a second type which contains groups which could interact with the radical centre of the enzyme.

The second approach was aided by a report from *Banerjee* and *Clapp* [39] which showed that *N*-alkylhydroxylamines were inhibitors of a plant lipoxygenase, and that the length of the alkyl chain was critical for good inhibitory potency. Based on our model (*Fig. 3*), we envisioned that the inhibitor would bind to the thio- or tyrosine radical of the enzyme *via* a one-electron bond. Substituted hydroxylamines of type **2** were prepared with a lipophilic chain designed to fit the hydrophobic pocket of 5-lipoxygenase and which might be anticipated to provide enzyme specificity.

Inhibitors of the Naphthalene-2-acetic-Acid Type. – The 7-alkoxynaphthalene-2-acetic acids were readily prepared as shown in *Scheme 3* from the corresponding 7-alkoxy-β-

Scheme 3. *Synthesis of Naphthalene-2-acetic-Acid Derivatives*

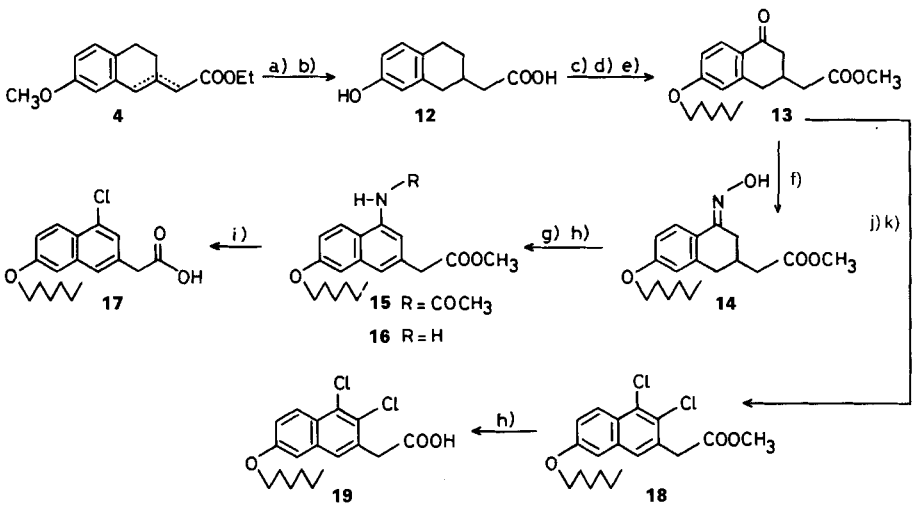


a) $(EtO)_2POCH(R^2)COOR^3/K(t\text{-BuO})/DMF$. *b)* Chloranil. *c)* KOH. *d)* HBr/AcOH. *e)* Alkyl halide/K_2CO_3.

tetralones, *e.g.* **3**, using ethyl (diethoxyphosphoryl)acetate or ethyl 2-(diethoxyphosphoryl)propionate and K(*t*-BuO) to form the esters (*e.g.*, **4** and **5**, respectively) in a *Wittig-Horner* reaction, followed by dehydrogenation to the naphthalene-ring system (→**6** and **7**, resp.) and then alkaline hydrolysis (→**10** and **11**, resp.). Selected derivatives (see, *e.g.*, **10** and **11**) were prepared by alkylation of the 7-hydroxynaphthalene-2-acetic acids **8** or **9**, which were available by ether cleavage of **6** and **7**, resp., with HBr/AcOH and saponification or directly *via* saponification of **6** and **7**.

Some chlorinated naphthalene-2-acetic acids were also prepared since halogen substitution in β-position to the acetic-acid substituent of many cyclooxygenase inhibitors significantly enhanced potency. The derivatives **17** and **19** were synthesized from the keto ester **13** which was available from **4** *via* hydrogenation, ether cleavage (→**12**), esterification, and oxidation of the alkoxy ester. As shown in *Scheme 4*, a Cl-atom was introduced at C(4) by treatment of the oxime **14** with Ac_2O/AcOH (→**15**) followed by hydrolysis (→**16**) and a *Sandmeyer* reaction on the resulting amine. Reaction of the keto ester **13** with PCl_5 resulted in the formation of the corresponding 3,4-dichloro-1,2-dihydronaphthalene which was dehydrogenated with S and hydrolysed to the naphthalene-2-acetic acid **19**.

Scheme 4. *Synthesis of Chlorinated Naphthalene-2-acetic Acids*

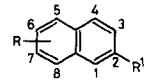


a) Pd/C, H_2. *b)* HBr/AcOH. *c)* MeOH/H^+. *d)* NaH/RBr. *e)* CrO_3/AcOH. *f)* $NH_2OH \cdot HCl/Et_3N$. *g)* AcOH/Ac_2O. *h)* EtOH/NaOH. *i)* $NaNO_2$/CuCl/HCl. *j)* PCl_5. *k)* S.

The results for lipoxygenase and cyclooxygenase inhibition shown in *Table 1* indicate that the potency of naphthalene-2-acetic acids as inhibitors of lipoxygenase depends on the length of the alkoxy substituent at C(7) and that compound **1** predicted to have the optimal chain length base on the model in *Fig. 3* is the best inhibitor[2]). In contrast to the structure-activity relationships for cyclooxygenase inhibitors where the α-methylated acetic acids are more potent, this substitution is detrimental for lipoxygenase inhibitors.

[2]) Compounds **1** and **21**–**23** were prepared similarly to **11** (see *Scheme 3*).

Table 1. *Lipoxygenase and Cyclooxygenase Inhibition by the Naphthalene-2-acetic Acids* **1**, **17**, **19**, **20**–**23**, *and Naproxen*



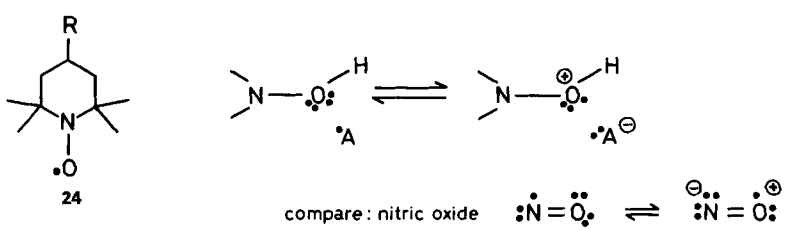
	R	R^1; further substituents	IC_{50} [μM]	
			5-Lipoxygenase	Cyclooxygenase
1	7-$CH_3(CH_2)_5O$	CH_2COOH	10	300
17	7-$CH_3(CH_2)_5O$	CH_2COOH; 4-Cl	70	500
19	7-$CH_3(CH_2)_5O$	CH_2COOH; 3,4-Cl_2	30	200
20 (= **11**)	7-CH_3O	$CH(CH_3)COOH$	≫ 100	500
21	7-$C_6H_5CH_2O$	$CH(CH_3)COOH$	50	500
22	7-$CH_3(CH_2)_5O$	$CH(CH_3)COOH$	80	200
23	7-$CH_3(CH_2)_2O$	CH_2COOH	> 100	> 100
Naproxen	6-CH_3O	$CH(CH_3)COOH$	> 100	2

For cyclooxygenase inhibitors, the equivalent of Cl-substitution at C(3) reduces potency whereas a Cl-atom at C(4) results in improved potency. The trends apply to lipoxygenase but are less pronounced. To improve potency of lipoxygenase inhibitors of this class, it will probably be necessary to replace the hexyloxy chain by more rigid groups of the same length, an approach which has been successful in the preparation of cyclooxygenase inhibitors from substituted phenylacetic acids.

Although the above compounds are relatively weak lipoxygenase inhibitors, the results strongly suggest that the 5-lipoxygenase specifically recognized the C(8) to C(20) moiety of arachidonic acid and that it would be possible to utilize the binding to this hydrophobic receptor to differentiate lipoxygenase from cyclooxygenase.

Hydroxylamines as 5-Lipoxygenase Inhibitors. – In a second series of inhibitors, the hydroxylamine group was used to interact with the radical-generating centre of the enzyme. The ability of hydroxylamines to form stable radicals *via* abstraction of a H-atom has been utilised in the preparation of compounds of the type **24** as spin-labelling

Scheme 5. *Hydroxylamine-Radical Interactions*



reagents (see *Scheme 5*). In the case of lipoxygenase, it was anticipated that an appropriately placed hydroxylamine residue in a substrate analogue would interact with the radical-generating centre of the enzyme *via* H-atom abstraction leading to reduced enzyme and oxidation products derived from the inhibitor. Alternatively, binding forces could be derived from an interaction between the electron lone pairs on the O-atom of the hydroxylamine with the radical to form a weak one-electron bond [36].

Banerjee and *Clapp* [39] reported the inhibition of a plant lipoxygenase by *N*-alkylhydroxylamines, a finding which was consistent with the above hypothesis that hydroxylamines may interact with the radical-generating centre of the enzyme. Of particular interest was their observation that the potency of the compounds as lipoxygenase inhibitors depended on the length of the alkyl chain and that the most effective inhibitor was the compound bearing a chain corresponding in length to that between the C-atom from which the H-radical was abstracted and the non-polar end of the unsaturated fatty-acid chain. In analogy, a series of *N*-alkylhydroxylamines was prepared and tested as 5-lipoxygenase and cyclooxygenase inhibitors. The compounds RNHOH **25–29** (see *Table 2*) were synthesized by alkylating hydroxylamine with alkyl halides.

Table 2. *Inhibition of 5-Lipoxygenase and Cyclooxygenase by the* N-*Alkylhydroxylamines RNHOH* **25–29**

	RNHOH R	IC_{50} [μM]	
		5-Lipoxygenase	Cyclooxygenase
25	$CH_3(CH_2)_9$	20	20
26	$CH_3(CH_2)_{10}$	20	30
27	$CH_3(CH_2)_{11}$	20	60
28	$CH_3(CH_2)_{12}$	10	50
29	$CH_3(CH_2)_{14}$	500	80

In addition, to test the effects of additional *N*- and *O*-alkylation, some derivatives were also prepared by alkylation of *O*-methyl- and/or *N*-methylhydroxylamines (see compounds R^1R^2N-OR **30–35** in *Table 3*).

Table 3. *Inhibition of 5-Lipoxygenase and Cyclooxygenase by the* N- *and/or* O-*Methylated Alkylhydroxylamines* $R^1R^2N-OR^3$ **30–35**

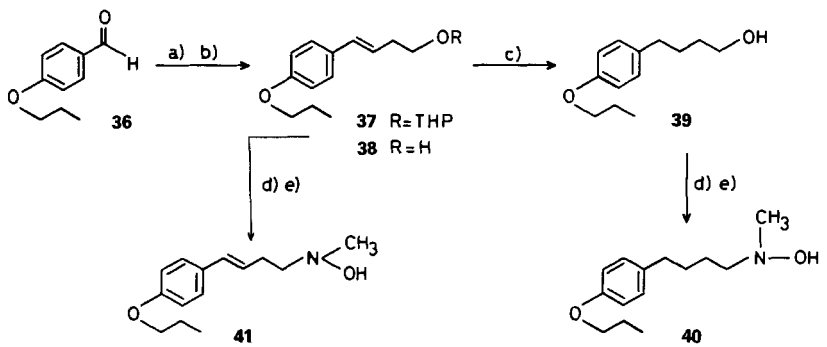
	$R^1R^2N-OR^3$			IC_{50} [μM]	
	R^1	R^2	R^3	5-Lipoxygenase	Cyclooxygenase
30	$CH_3(CH_2)_{10}$	H	CH_3	50	3
31	$CH_3(CH_2)_{10}$	CH_3	H	0.8	20
32	$CH_3(CH_2)_{10}$	CH_3	CH_3	60	> 100
33	$CH_3(CH_2)_{11}$	CH_3	H	0.8	20
34	$CH_3(CH_2)_{11}$	H	CH_3	100	1
35	$CH_3(CH_2)_{11}$	CH_3	CH_3	100	200

Table 2 shows the inhibition of the *N*-alkylhydroxylamines **25–29** on 5-lipoxygenase and cyclooxygenase. Although the C_{12}-chain compound was among the most active derivatives as predicted, there was little discrimination due to the length of the alkyl chains, except for very long *N*-alkylhydroxylamines. There was also little differentiation between cyclooxygenase and lipoxygenase by these compounds. A possible explanation was the high flexibility of the alkyl chains, and more rigid analogues were then designed. The most striking effects were those of additional *N*- and *O*-methylation. Thus, for **30–35**, dramatic changes in enzyme specificity were produced *(Table 3)*. *O*-Alkylation reduced potency as 5-lipoxygenase inhibitors but increased activity against cyclooxygenase, whereas *N*-methylation had the reverse effect. Methylation on both the N- and O-atom decreased potency towards both enzymes.

In an attempt to further improve specificity for 5-lipoxygenase, the alkyl chain of the hydroxylamine derivatives was modified so as to reduce mobility and to constrain it in a conformation approximating that for C(8) to C(20) of the substrate arachidonic acid in the enzyme active site. To this end, aromatic rings were introduced to mimic olefinic linkages.

Thus, the hydroxylamines **40** and **41** were prepared from 4-propoxybenzaldehyde (**36**). *Wittig* reaction of **36** with {3-[(tetrahydro-2*H*-pyran-2-yl)oxy]propyl}triphenylphosphonium bromide and K(*t*-BuO) gave **37** *(Scheme 6)*, and acidic removal of the tetrahydropyranyl protecting group yielded the alcohol **38** which could be hydrogenated to **39**. From **38** and **39**, **41** and **40**, respectively, were prepared *via* mesylation and reaction with *N*-methylhydroxylamine.

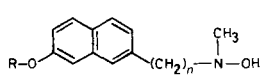
Scheme 6. *Synthesis of* N-*[(4-Alkoxyphenyl)alkyl or -alkenyl]hydroxylamines*



a) {[3-(Tetrahydro-2*H*-pyran-2-yl)oxy]propyl}triphenylphosphonium bromide/K(*t*-BuO). *b)* HCl. *c)* Pd/C, H_2. *d)* $MsCl/Et_3N$. *e)* MeNHOH·HCl.

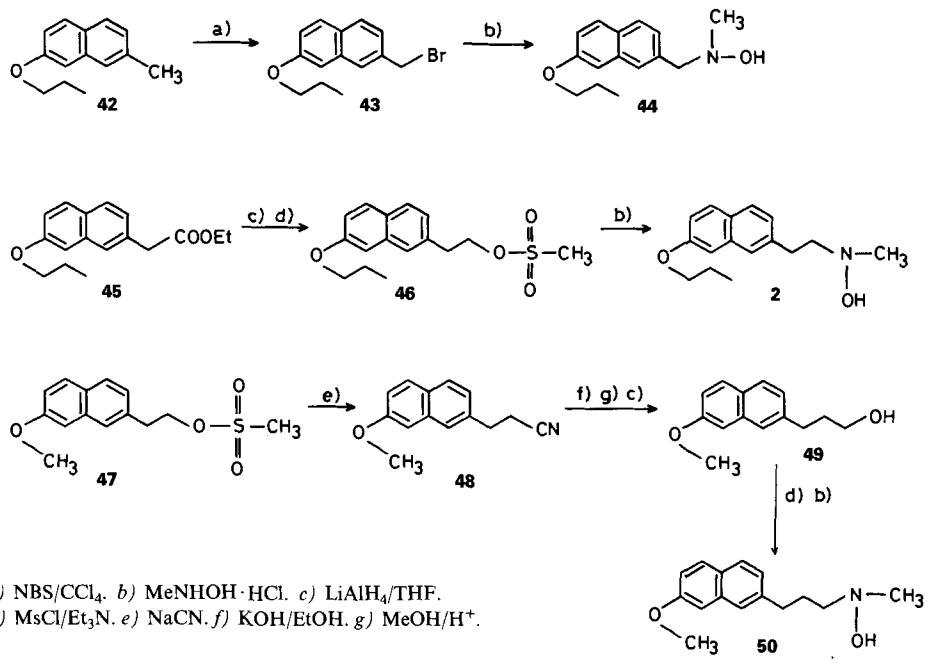
Moreover, 2,7-disubstituted naphthalene moieties were used to mimic a (*Z*,*Z*)-2,6-hexadiene unit of the substrate. The 2,7-disubstituted naphthalene derivatives, *e.g.* **44**, **2**, and **50**–**55** (see *Table 4*) were prepared *via* reaction of the corresponding naphthalenealkyl halides or methanesulfonates with the appropriate hydroxylamine derivative as exemplified by **43**→**44** and **46**→**2**, respectively *(Scheme 7)*. The starting 7-alkoxynaph-

Table 4. *Inhibition of 5-Lipoxygenase and Cyclooxygenase by the* N-*(7-Alkoxynaphthalene-2-alkyl)hydroxylamines* **2**, **44**, *and* **50**–**55**



	R	*n*	IC_{50} [μM]	
			5-Lipoxygenase	Cyclooxygenase
50	CH_3	3	0.8	30
51	CH_3CH_2	2	1.0	50
2	$CH_3(CH_2)_2$	2	0.4	50
52	$CH_3(CH_2)_3$	2	1.0	50
53	$CH_3(CH_2)_4$	2	20	100
44	$CH_3(CH_2)_2$	1	0.9	50
54	$CH_3(CH_2)_3$	1	0.5	30
55	$CH_3(CH_2)_4$	1	1.0	50

Scheme 7. *Synthesis of N-(7-Alkoxynaphthalene-2-alkyl)hydroxylamines*



a) NBS/CCl_4. *b)* MeNHOH·HCl. *c)* $LiAlH_4$/THF.
d) MsCl/Et_3N. *e)* NaCN. *f)* KOH/EtOH. *g)* MeOH/H^+.

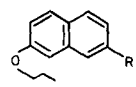
thalene-2-alkyl halides and methanesulfonates were synthesized by bromination of 2-alkoxy-7-alkylnaphthalene (*e.g.* **42**→**43**) and by reduction of 7-alkoxynaphthalene-2-acetates followed by mesylation (*e.g.* **45**→**46**) or by a sequence *via* the methanesulfonate of 7-alkoxynaphthalene-2-ethanols and the corresponding nitrile (*e.g.* **47**→**48**→**49**, *Scheme 7*), respectively.

The incorporation of a phenyl or a styryl group into the *N*-dodecylhydroxylamine structure had little effect on potency or selectivity as compared to the more flexible *N*-alkylhydroxylamines (**40** and **41**: IC_{50} (5-lipoxygenase), 1 and 0.7 μM, resp.; IC_{50}(cyclooxygenase), 50 and 30 μM, resp.), whereas 2,7-disubstituted naphthalenes improved potency by a factor of 4 *(Table 4)*. Although variation from the predicted optimum chain length did reduce potency, the effects were not dramatic if only one or two C-atoms were involved. The optimal compound appeared to be *N*-methyl-*N*-(7-propoxynaphthalene-2-ethyl)hydroxylamine (**2**), and further variation of this structure was undertaken.

Thus, we investigated the effects on lipoxygenase inhibitory potency produced by replacing the *N*-methyl group of **2** by larger alkyl residues and by chains that would either mimic the C(1) to C(6) portion of arachidonic acid or that could potentially interact with the Fe^{3+} ion postulated to be in the enzyme active site according to our model *(Fig. 3)*. To this end, the *N*-isopropyl, *N*-cyclohexyl, and *N*-dodecyl derivatives **56**–**58** (see *Table 5*) were prepared by a procedure analogous to that shown in *Scheme 7* (see formation of **2**). The hydrazides **59**–**61** (see *Table 5*) were synthesized *via* alkylation of **2** with the appropriate bromo ester followed by reaction with hydrazine hydrate in EtOH, whereas the

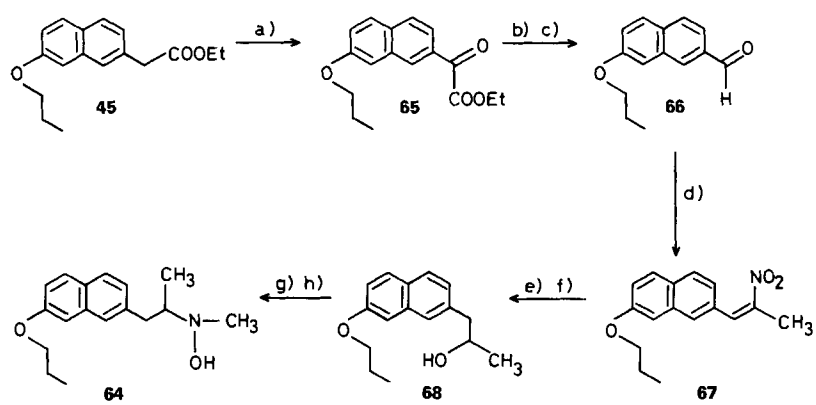
carboxylate **62** (see *Table 5*) was obtained by alkaline hydrolysis of the corresponding ester. The effect of branching of the *N*-ethylhydroxylamine chain on 5-lipoxygenase inhibitory potency was explored with the derivatives **63** and **64** (see *Table 5*). Compound **63** was prepared from α-methyl-7-propoxynaphthalene-2-acetate analogously to the methods shown in *Scheme 7* (see formation of **2**), and the derivative **64** could be synthesized from ethyl 7-propoxynaphthalene-2-acetate (**45**) *via* **65**–**68** as shown in *Scheme 8*.

Table 5. *Inhibition of 5-Lipoxygenase and Cyclooxygenase by the 2-Substituted 7-Propoxynaphthalene Derivatives* **2** *and* **56**–**64**



	R	IC_{50} [μM]	
		5-Lipoxygenase	Cyclooxygenase
2	$CH_2CH_2N(OH)-CH_3$	0.4	50
56	$CH_2CH_2N(OH)-CH(CH_3)_2$	0.7	50
57	$CH_2CH_2N(OH)-$(Cyclohexyl)	6	100
58	$CH_2CH_2N(OH)-(CH_2)_{11}CH_3$	≫ 100	≫ 100
59	$CH_2CH_2N(OH)-CH_2CONHNH_2$	7	> 100
60	$CH_2CH_2N(OH)-(CH_2)_3CONHNH_2$	8	300
61	$CH_2CH_2N(OH)-(CH_2)_5CONHNH_2$	8	300
62	$CH_2CH_2N(OH)-(CH_2)_5COONa$	40	≫ 100
63	$CH(CH_3)CH_2N(OH)-CH_3$	2	200
64	$CH_2CH(CH_3)N(OH)-CH_3$	2	100

Scheme 8. *Synthesis of* N-*(7-Alkoxy-α-methylnaphthalene-2-alkyl)hydroxylamines*



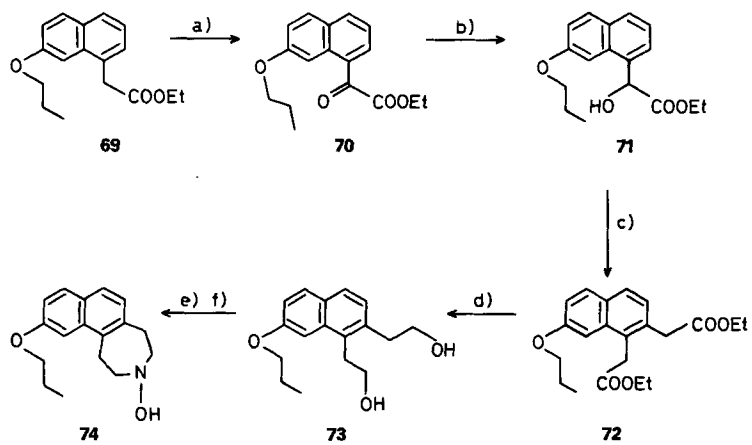
a) SeO_2. *b)* NaOH. *c)* Aniline. *d)* $EtNO_2/NH_4OH$. *e)* *Raney*-Ni. *f)* $NaBH_4$. *g)* $MsCl/Et_3N$. *h)* MeNHOH·HCl.

The results for inhibition of 5-lipoxygenase and cyclooxygenase by **56**–**64** show that only small *N*-alkyl groups are tolerated in place of the *N*-methyl group of **2** without a significant loss of inhibitory potency (see *Table 5*). The reduction of activity by adding a chain which corresponds to C(1) to C(6) of arachidonic acid or by adding a hydrazide which could potentially coordinate with the Fe^{3+} ion was initially surprising. Possibly, the binding of such substituents forces the hydroxylamine group into a conformation where it cannot optimally interact with the radical-generating centre of the enzyme. Probably

for similar reasons, **63** and **64** with a β- and α-methyl group, respectively, are less potent derivatives.

To fix the *N*-ethylhydroxylamine chain of **2** so that its N-atom would lie directly over the position of the predicted radical-generating centre of the enzyme, the cyclic hydroxylamine derivative **74** was prepared. Ethyl 7-propoxynaphthalene-1-acetate (**69**) was oxidised to the keto ester **70** with SeO_2, reduced to the corresponding hydroxy ester **71**, and then treated with triethyl orthoacetate as described by *Raucher et al.* [41] to produce the mixed orthoester followed by elimination of EtOH and a *Claisen* rearrangement to give the diacetate **72**. Reduction of **72** with $LiAlH_4$ and reaction of the resulting diol **73** with MsCl in pyridine at 0° produced the dimesylate which was cyclised to the azepin-*N*-ol **74** with $NH_2OH \cdot HCl$ in EtOH.

Scheme 9. *Synthesis of Azepin-* N-*ol* **74**

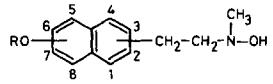


a) SeO_2. *b)* $NaBH_4$. *c)* Triethyl orthoacetate/185°. *d)* $LiAlH_4$. *e)* MsCl/pyridine. *f)* $NH_2OH \cdot HCl$.

Azepin-*N*-ol **74**, although designed to restrict the rotation of the *N*-ethylhydroxylamine chain of **2** (see above), is less active than **2** (IC_{50} (**74**) = 5 and 500 μM for 5-lipoxygenase and cyclooxygenase, resp.), probably because the N–OH bond is now equatorial and not directed towards the predicted position of the radical-generating centre according to our enzyme model. Thus, a loss rather than a gain of 5-lipoxygenase inhibitory activity is observed.

A further series of hydroxylamines parent to **2** explored the effect of varying the position of the alkoxy and *N*-ethylhydroxylamine moieties on the naphthalene ring. *Table 6* shows the inhibitory potency of compounds **75–82** (prepared like **2**, see *Scheme 7*) against 5-lipoxygenase and cyclooxygenase. The position of substitution is not critical, but loss in inhibitory potency is observed in those compounds in which the conformation of the substituents does not allow the critical elements for binding to the enzyme (*i.e.* the (*Z*)-double-bond equivalents, the terminal alkyl chain, and the hydroxylamine O-atom) to adopt the spacial arrangement for these groups corresponding to the one when substrate is bound to 5-lipoxygenase.

Table 6. *Inhibition of 5-Lipoxygenase and Cyclooxygenase by the N-(Naphthalenealkyl)hydroxylamine Derivatives* **2** *and* **75–82**



	R	Position of		IC_{50} [μM]	
		RO	$CH_2CH_2N(OH)CH_3$	5-Lipoxygenase	Cyclooxygenase
75	$CH_3(CH_2)_2$	6	1	0.7	60
76	$CH_3(CH_2)_3$	6	1	2	200
77	$CH_3(CH_2)_2$	6	2	2	30
78	$CH_3(CH_2)_4$	6	2	3	30
79	$CH_3(CH_2)_2$	7	1	5	10
2	$CH_3(CH_2)_2$	7	2	0.4	50
80	$CH_3(CH_2)_2$	8	1	300	100
81	$CH_3(CH_2)_2$	8	2	0.4	50
82	$CH_3(CH_2)_3$	8	2	0.6	100

Discussion. – Based on mechanistic considerations, a 3-dimensional model of potential substrate binding and catalytic functions in the active site of 5-lipoxygenase has been developed and used to design two types of lipoxygenase inhibitors. In the naphthalene-2-acetic-acid series, it was shown that the nature and position of the alkoxy substituent on the naphthalene ring determined the specificity of the inhibitor for 5-lipoxygenase over cyclooxygenase. From the limited amount of data presented here, it would appear that arylacetic acids which have a lipophilic surface corresponding to the 'convex edge' of the C(6) to C(20) moiety of arachidonic acid are likely to be selective inhibitors, *e.g.* **1**. Possibly better inhibitors than **1** can be prepared by restricting the conformational freedom of the alkoxy chain.

A second series of inhibitors utilised a hydroxylamine group to interact with a postulated radical centre in the enzyme active site. For this class of inhibitors, addition of a lipophilic chain corresponding to the C(8) to C(20) moiety of arachidonic acid produced the most selective and potent inhibitors for 5-lipoxygenase, but because the hydroxylamine function proved the dominant binding interaction, as long as the lipophilic group approximated the properties of the corresponding part of the substrate molecule, good inhibition was obtained. Minor deviations from the structure of the best inhibitor, **2**, appeared to be less critical. Alternatively, other binding modes such as one in which the hydroxylamine function coordinates with the Fe^{3+} ion could complicate the interpretation of the results. Structural variation near the hydroxylamine group has a more pronounced effect on inhibitory potency. Substitution on the N-atom with small alkyl groups (Me, i-Bu) enhanced activity, but attempts to utilise the binding interactions to C(1) to C(7) of arachidonic acid reduced activity, presumably because the dominant interaction of the hydroxylamine function with the enzyme was then compromised.

Whether the hydroxylamine group interacts with the enzyme by forming a partial one-electron bond, or by donating a H-radical thereby reducing the radical centre of the enzyme, or by a mechanism involving interaction with the Fe^{3+} ion is unknown. The mechanism quoted above was used as a basis for drug design, and although it led to active compounds, it remains a hypothesis. An alternative view of the mechanism of inhibition of lipoxygenases by hydroxylamine derivatives has been proposed by *Clapp et al.* [39].

Experimental Part

Enzyme Inhibition Assays. – *Prostaglandin Synthetase.* Prostaglandin synthesis was tested using a microsomal fraction from bull seminal vesicles as the enzyme source. The tissue was homogenised in 2 volumes of 0.1M sodium-phosphate buffer (pH 7.0) with a *Waring* blender. The homogenate was centrifuged at 5500 *g* for 20 min, and the microsomes were obtained from the supernatant by centrifugation at 75000 *g* for 90 min. Finally, the microsomal pellet was resuspended in a small volume of dist. H_2O and lyophilised. Prior to use, the microsomes were suspended in 0.1M sodium-phosphate buffer (pH 7.4) at a concentration of 3 mg/ml. The test compound was dissolved in DMSO at a concentration of 10^{-2}M and diluted to the desired concentration with 0.1M sodium-phosphate buffer (pH 7.4). Then, 100 µl of the appropriate dilution were preincubated for 5 min at 37° with 700 µl of microsomal suspension and 100 µl of 10 mM reduced glutathione, and the reaction was started by addition of 100 µl of 0.33 mM [1-^{14}C]arachidonic acid (*ca.* 120000 cpm, *Amersham Buchler GmbH & Co. KG*, D–3300 Braunschweig, FRG). Heat-inactivated microsomes were used as negative control. After 30 min incubation at 37°, the reaction was stopped by addition of 500 µl of 1M acetate buffer (pH 4.0)/0.167M HCl 1:4 (final pH 3.0), and the products were immediately extracted with 5 ml of AcOEt, after which the org. phase was removed and dried (Na_2SO_4) for 15 min. A 4.0-ml sample was taken, an additional 200 µl removed to determine recovery of radioactivity, 10 µl each of $PGF_{2\alpha}$ and PGE_2 (1 mg/ml) added, and the whole extract evaporated at 37° under N_2. The residue was taken up in 70 µl of $CHCl_3$/MeOH 2:1, transferred quantitatively to silica gel *60* F_{254} TLC plates (*Merck*, Darmstadt, FRG), and developed with benzene/dioxane/AcOH 50:50:2. $PGE_{2\alpha}$ and PGF_2 were then made visible with I_2 vapour, scraped from the plates, and, after addition of 4 ml of *Rialuma* (*Lumac/3M bv*, 6372 Schaesberg, The Netherlands), counted in a *Packard-2000CA-TRI-CARB* liquid scintillation counter. HMPA = hexamethylphosphorous triamide.

Lipoxygenase. Human neutrophils from normal donor blood were isolated according to *Markert et al.* [42]. The test compound was dissolved in DMSO at a concentration of 10^{-2}M and diluted to the desired concentration with phosphate-buffered saline (p.-b.s.). The maximum DMSO concentration in the final assay never exceeded 1%. At 37°, 2×10^7 cells in 300 µl of p.-b.s. were preincubated for 5 min with various concentrations of test substance. Then, 100 µl of 20 µM calcium ionophore *A23187* were added and, after 2 min at 37°, 100 µl of 0.16 mM [1-^{14}C]arachidonic acid (*ca.* 120000 cpm). The incubation was continued for further 4 min at 37° and the reaction stopped by the addition of 1.0 ml of MeOH. The tubes were then centrifuged for 5 min at 1225 *g* and the supernatants removed. The pellets were resuspended in 250 µl of MeOH and recentrifuged for 5 min at 1225 *g*. The supernatants were combined, brought to pH 3.0 with 1N HCl and 3.0 ml of Et_2O, and 1.0 ml of H_2O added. After shaking mechanically for 10 min, the phases were allowed to separate, and the Et_2O layer was removed and dried (Na_2SO_4) for 10 min. After removing 200 µl to measure recovery of radioactivity, 2.0-ml samples were taken, 0.5 ml of abs. EtOH added, and the mixture evaporated under N_2. The residues were taken up in 70 µl of $CHCl_3$/MeOH 2:1, transferred quantitatively to silica gel *60* F_{254} TLC plates (*Merck*, Darmstadt, FRG), and developed with AcOEt/isooctane/AcOH/H_2O 165:75:30:150. The radioactive spots were located by radio-scanning and quantified by liquid scintillation counting.

Synthetic Procedures. – *Ethyl 7-Methoxynaphthalene-2-acetate* (**6**). To ethyl (diethoxyphosphoryl)acetate (21 g) in DMF (120 ml), K(*t*-BuO) (20.5 g) was added in 3 portions during 30 min. Then, *3,4-dihydro-7-methoxynaphthalen-2(1H)-one* (**3**; 20.2 g) in toluene (100 ml) was slowly added and the temp. rose to 40°. The soln. was stirred for 2 h at 40°, then 15% AcOH/H_2O (80 ml) was added. After stirring for another 30 min, the soln. was poured into H_2O (300 ml) and extracted 3 times with Et_2O. The Et_2O extracts were dried ($MgSO_4$), filtered, and evaporated. The red oily residue was chromatographed on silica gel with Et_2O/hexane 1:1: 17 g (60%) of *ethyl 3,4-dihydro-7-methoxynaphthalene-2-acetate* (**4**). The clear oil and chloranil (25.8 g) in xylene (150 ml) was heated under reflux for 4 h. After evaporation, the dark residue was chromatographed on silica gel with hexane/Et_2O 9:1: 7.5 g (44%) of **6** as pale brown resin. Anal. calc. for $C_{15}H_{16}O_3$ (244.25): C 73.74, H 6.60, O 19.65; found: C 73.51, H 6.60, O 19.85.

Compounds **8** and **10** were prepared like **9** and **11** (= **20**), respectively (see below).

7-Propoxynaphthalene-2-ethanol. A soln. of **6** (7 g) in CH_2Cl_2 (60 ml) under Ar was cooled to −10°, BBr_3 (5.5 ml) added dropwise so that the temp. did not rise above −5°, and the soln. stirred at −10° for further 2 h and cautiously poured into ice-water (400 ml). The formed *ethyl 7-hydroxynaphthalene-2-acetate* (6.7 g, 100%) was filtered off, dried (m.p. 137–139°), and then dissolved in isobutyl methyl ketone (60 ml). After addition of PrBr (4.3 g), HMPA (5 ml), and K_2CO_3 (8 g), the mixture was refluxed for 20 h, filtered, and evaporated. The remaining oil was dissolved in Et_2O, washed 3 times with H_2O, dried ($MgSO_4$), and evaporated: 7.4 g (93%) of *propyl 7-propoxynaphthalene-2-acetate.* The pale brown oil in THF (100 ml) was added dropwise to a suspension of $LiAlH_4$ (2.07 g) in THF (100 ml) at r.t. and stirred for 2 h at r.t. Then, H_2O (15 ml) in THF (100 ml) was added

dropwise. The mixture was stirred for further 30 min at r.t., then filtered, and the residue washed twice with THF. The THF solns. were dried ($MgSO_4$) and evaporated. Recrystallisation from Et_2O/hexane gave 4.35 g (69%) of *7-propoxynaphthalene-2-ethanol* as pale crystals. M.p. 95–97°. Anal. calc. for $C_{15}H_{18}O_2$ (230.30): C 78.23, H 7.88, O 13.89; found: C 77.95, H 7.64, O 13.82.

N-*Methyl*-N-*(7-propoxynaphthalene-2-ethyl)hydroxylamine* (**2**). To a soln. of 7-propoxynaphthalene-2-ethanol (10 g) in pyridine (10 ml) at 0°, MsCl (15 ml) was added dropwise within 15 min, the yellow suspension stirred for 2 h at 0°, then poured into H_2O (500 ml), and the white crystalline product filtered off, washed with H_2O, and dried giving 13.8 g (100%) of *7-propoxynaphthalene-2-ethyl methanesulfonate* (**46**). M.p. 93–95°. A mixture of **46** (13.8 g), $NH_2OH \cdot HCl$ (17 g), Et_3N (40 ml), and EtOH (400 ml) was heated under reflux for 18 h. After evaporation, the white residue was extracted 3 times with Et_2O, the Et_2O extract washed with H_2O, dried ($MgSO_4$), and evaporated to yield 6.0 g (51%) of **2**. M.p. 113–115° (from Et_2O). Anal. calc. for $C_{16}H_{21}NO_2$ (259.35): C 74.10, H 8.06, N 5.38, O 12.30; found: C 73.92, H 8.12, N 5.30, O 12.10.

In analogy to the above procedure, **50–53**, **56–58**, **63**, **64**, and **75–83** were prepared (see *Table 7*). Compound **47** (m.p. 81–82° (from Et_2O)) was prepared like **46**.

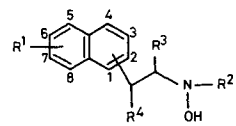


Table 7. N-*(Alkoxynaphthalenealkyl)hydroxylamines Obtained from the Corresponding Alkanols after Mesylation and Reaction with $NH_2OH \cdot HCl$*

	R^1	R^2	R^3	R^4	*n*	M.p. [°]	Yield [%]
2	7-$CH_3(CH_2)_2O$	CH_3	H	H	2	113–115	51
51	7-CH_3CH_2O	CH_3	H	H	2	115–117	39
52	7-$CH_3(CH_2)_3O$	CH_3	H	H	2	103–105	51
53	7-$CH_3(CH_2)_4O$	CH_3	H	H	2	170–172[a])	50
56	7-$CH_3(CH_2)_2O$	$(CH_3)_2CHCH_2$	H	H	2	82–83	22
57	7-$CH_3(CH_2)_2O$	cyclohexyl	H	H	2	114–115	34
58	7-$CH_3(CH_2)_2O$	$CH_3(CH_2)_{11}$	H	H	2	83–85	48
63	7-$CH_3(CH_2)_2O$	CH_3	H	CH_3	2	92–94	45
64	7-$CH_3(CH_2)_2O$	CH_3	CH_3	H	2	93–95	26
75	6-$CH_3(CH_2)_2O$	CH_3	H	H	1	98–100	37
76	6-$CH_3(CH_2)_3O$	CH_3	H	H	1	79–81	62
77	6-$CH_3(CH_2)_2O$	CH_3	H	H	2	115–117	60
78	6-$CH_3(CH_2)_4O$	CH_3	H	H	2	110–112	58
79	7-$CH_3(CH_2)_2O$	CH_3	H	H	1	103–104	56
80	8-$CH_3(CH_2)_3O$	CH_3	H	H	1	79–81	62
81	8-$CH_3(CH_2)_2O$	CH_3	H	H	2	93–95	29
82	8-$CH_3(CH_2)_3O$	CH_3	H	H	2	109–111	46
83	7-$CH_3(CH_2)_2O$	H	H	H	2	136–138	30

[a]) Hydrochloride.

7-(Benzyloxy)-α-methylnaphthalene-2-acetic Acid (**21**). To a soln. of *3,4-dihydro-7-methoxynaphthalen-2(1H)-one* (**3**; 31 g) in toluene (100 ml) was added methyl (diethoxyphosphoryl)propionate (47 g) in toluene (500 ml), followed by K(*t*-BuO) (21.6 g). The mixture was heated at 100° for 7 h, cooled, poured in H_2O (1 l), and acidified to pH 3 with HCl. The org. phase was separated, the aq. phase extracted 3 times with Et_2O, and the combined org. phase dried ($MgSO_4$) and evaporated. The residual oil was chromatographed on silica gel with toluene/AcOEt 9:1, giving 21 g (48%) of a yellow oil which was heated with 10% Pd/C (1.1 g) in decalin (50 ml) for 16 h at 190°. After cooling, the soln. was filtered and the decalin removed under reduced pressure. The crude residue was recrystallised from EtOH/Et_2O giving 16.6 g (80%) of *methyl 7-methoxy-α-methylnaphthalene-2-acetate* (**7**; m.p. 66–69°) which was dissolved in MeOH (100 ml) together with KOH (15.2 g) and H_2O (15 ml). The mixture was heated under reflux at 70° for 3 h, then evaporated and the residue dissolved in 250 ml of H_2O. The starting material was removed by extraction with Et_2O, the aq. phase then acidified with HCl and extracted 3 times with Et_2O. The Et_2O soln. was dried ($MgSO_4$) and concentrated. Crystallisation from Et_2O gave 10.4 g (66.7%) of *7-methoxy-α-methylnaphthalene-2-acetic acid* (**11** ≡ **20**) as a brown powder. M.p. 133–135°. Compound **11** was dissolved in AcOH (50 ml) and heated under reflux with 25 ml of 62% HBr in H_2O at 130° for 2 h. The dark oil obtained after

evaporation was chromatographed on silica gel with Et_2O/CH_2Cl_2 1:1: 7.25 g (82%) of *7-hydroxy-α-methylnaphthalene-2-acetic acid* (**9**). M.p. 166–168°, after recrystallisation from Et_2O. To a soln. of **9** in THF/HMPA 2:1 (375 ml), NaH (55%; 4.0 g) was added, the mixture warmed to 60°, and benzyl bromide (2 ml) added. After cooling to r.t., the mixture was stirred for 10 h, H_2O (50 ml) added dropwise, the mixture acidified with HCl, diluted with H_2O (500 ml), and extracted with CH_2Cl_2. The org. extract was dried and evaporated. To a soln. of the crude product in MeOH (100 ml), KOH (15 g) in H_2O (50 ml) was added, the mixture stirred at 60° for 4 h, then evaporated, the residual oil diluted with H_2O (1 l), and the mixture extracted once with Et_2O (200 ml). The aq. phase was acidified with HCl, extracted with CH_2Cl_2, and the org. extract dried ($MgSO_4$) and evaporated. Recrystallisation from Et_2O/hexane yielded 2.25 g (21%) of **21**. M.p. 150–151°. Anal. calc. for $C_{20}H_{18}O_3$ (306.36): C 78.42, H 5.90, O 15.69; found: C 78.30, H 6.00, O 15.34.

Of the starting material **9**, 5.5 g were recovered.

In analogy to the above procedure, **22**, **23** and **1** were prepared.

7-(Hexyloxy)-α-methylnaphthalene-2-acetic Acid (**22**): m.p. 105–106°. Yield 48%. Anal. calc. for $C_{19}H_{24}O_3$ (300.40): C 76.02, H 8.14, O 15.90; found: C 76.22, H 8.00, O 16.05.

7-Propoxynaphthalene-2-acetic Acid (**23**): m.p. 177–179°. Anal. calc. for $C_{15}H_{16}O_3$ (244.26): C 73.75, H 6.60, O 19.64; found: C 73.70, H 6.62, O 19.68.

7-(Hexyloxy)naphthalene-2-acetic Acid (**1**): m.p. 164–167°. Yield 54%. Anal. calc. for $C_{18}H_{24}O_3$ (288.39): C 74.96, H 8.39, O 16.64; found: C 75.20, H 8.62, O 16.83.

1,2,3,4-Tetrahydro-7-hydroxynaphthalene-2-acetic Acid (**12**). A soln. of ethyl 3,4-dihydro-7-methoxynaphthalene-2-acetate (**4**; 60 g) in EtOH (500 ml) was hydrogenated for 7 h using 10% Pd/C (6 g) at 50° and 5 atm. After cooling and evaporation, 59 g (97%) of *ethyl 1,2,3,4-tetrahydro-7-methoxynaphthalene-2-acetate* were obtained as a dark oil. To its soln. in 500 ml of AcOH, HBr (62% in H_2O; 81 ml) was added, the mixture heated for 4 h at 100°, then evaporated, and the residual oil crystallised, after addition of Et_2O. The crystals were washed with cold Et_2O and dried to give 33 g (67%) of **12**. M.p. 146–148°. Anal. calc. for $C_{12}H_{14}O_3$ (206.24): C 69.88, H 6.84, O 23.27; found: C 69.72, H 6.76, O 23.14.

Methyl 7-(Hexyloxy)-1,2,3,4-tetrahydro-4-(hydroximino)naphthalene-2-acetate (**14**). To a soln. of **12** (40 g) in MeOH (500 ml) conc. H_2SO_4 (2.7 ml) was added and refluxed for 3 h. The soln. was evaporated, the residue dissolved in AcOEt, washed with aq. $NaHCO_3$ soln., dried ($MgSO_4$), and evaporated: 43.8 g (100%) of *methyl 1,2,3,4-tetrahydro-7-hydroxynaphthalene-2-acetate*. A soln. of 43.8 g of this ester in HMPT (150 ml) was added dropwise to NaH (80%; 6.6 g) in HMPT (150 ml). The mixture was heated to 40° and stirred for 30 min. To the brown suspension, bromohexane (42 ml) in THF (250 ml) was added dropwise, the mixture heated to 70° for 2 h, cooled, poured into 1N HCl (1 l), and extracted with Et_2O. The extract was washed twice with H_2O, dried ($MgSO_4$), and evaporated. The crude oil was chromatographed on silica gel with Et_2O/hexane 19:1: 48.3 g (79.9%) of *methyl 7-(hexyloxy)-1,2,3,4-tetrahydronaphthalene-2-acetate*. This green-yellow oil in AcOH (1.5 l) was cooled to 5° and a soln. of Cr_2O_3 (71.6 g) in H_2O (20 ml) and AcOH (350 ml) added dropwise (it is important that the CrO_3 soln. never rises over 5°!). The mixture was stirred for 2 h at r.t. Then, MeOH (85 ml) was added, the mixture poured into H_2O (3,5 l) and extracted with Et_2O, and the extract dried ($MgSO_4$) and evaporated: 62.5 g (98%) of *methyl 7-(hexyloxy)-1,2,3,4-tetrahydro-4-oxonaphthalene-2-acetate* (**13**). To this yellow oil in EtOH (1.5 l), $NH_2OH \cdot HCl$ (142 g) and AcONa (37 g) in H_2O (200 ml) were added. The soln. was heated under reflux for 3 h, then evaporated, H_2O (1 l) added, and the crystalline precipitate filtered off and dried: 64.5 g (98.5%) of **14**. M.p. 80–82°. Anal. calc. for $C_{19}H_{27}NO_4$ (333.43): C 68.44, H 8.16, N 4.20, O 19.19; found: C 68.21, H 8.25, N 4.38, O 19.32.

Methyl 4-(Acetylamino)-7-(hexyloxy)naphthalene-2-acetate (**15**). A soln. of **14** (10 g) in AcOH (160 ml) and Ac_2O (20 g) was refluxed for 7 h under a constant stream of HCl. The gas stream was then stopped, the mixture stirred for 16 h at 100°, the solvent removed, the residue poured into 0.2N NaOH (500 ml) mixed with ice and extracted with CH_2Cl_2 to give a dark oil. Purification on silica gel with hexane/Et_2O 9:1 gave 6.8 g (71%) of **15** which crystallised from EtOH/Et_2O as a pale yellow powder. M.p. 87–92°. Anal. calc. for $C_{21}H_{27}NO_4$ (357.45): C 70.56, H 7.62, N 3.92, O 17.90; found: C 70.42, H 7.72, N 3.98, O 17.72.

4-Amino-7-(Hexyloxy)naphthalene-2-acetic Acid. To a soln. of **15** (1.4 g) in EtOH (20 ml), a 30% NaOH soln. (8 ml) was added. The mixture was refluxed for 2 h, poured into H_2O, and the crystalline precipitate filtered off and washed with H_2O and then with Et_2O: 1.2 g of the Na salt of the title compound. M.p. 208° (dec.). Anal. calc. for $C_{18}H_{23}NO_3$ (301.39): C 71.73, H 7.69, N 4.65, O 15.92; found: C 71.84, H 7.73, N 4.74, O 16.21.

4-Chloro-7-(hexyloxy)naphthalene-2-acetic Acid (**17**). To the above Na salt (0.6 g) suspended in H_2O (5 ml), $NaNO_2$ (0.13 g) was added and the mixture cooled to 0°. Within 15 min, conc. HCl (1 ml) in AcOH (2 ml) was added dropwise and the resulting soln. stirred for 1 further h at 0°. The soln. was then added dropwise into 3 ml of conc. HCl soln. containing 0.55 g of Cu(I)Cl. The mixture was allowed to return to r.t. and stirred for 2 h before warming to 60° and stirring for another h. After cooling, the mixture was poured into H_2O (100 ml), the dark

precipitate filtered off, and the aq. phase extracted with CH_2Cl_2. The org. extract was dried ($MgSO_4$) and evaporated and the residue chromatographed on silica gel using CH_2Cl_2/MeOH 95:5, to give 0.25 g (41%) of **17**. M.p. 100–102°. Anal. calc. for $C_{18}H_{21}ClO_3$ (320.82): C 67.41, H 6.53, Cl 11.02, O 15.01; found: C 67.24, H 6.52, Cl 10.82, O 15.22.

3,4-Dichloro-7-(hexyloxy)naphthalene-2-acetic Acid (**19**). Under Ar, PCl_5 (3.9 g) was added to **13** in benzene (50 ml). The mixture was stirred at r.t. for 4 h, then poured into H_2O (100 ml), and extracted with Et_2O. The combined extract was washed with $NaHCO_3$ soln., dried ($MgSO_4$), and evaporated, and the residual yellow pale oil chromatographed on silica gel with hexane/Et_2O 1:1: 1.5 g (40%) of *methyl 3,4-dichloro-7-(hexyloxy)-1,2-dihydronaphthalene-2-acetate*. This pale yellow oil was heated together with S (140 mg) for 3 h at 240°. After chromatography on silica gel with hexane/Et_2O 9:1, 0.5 g of methyl *3,4-dichloro-7-(hexyloxy)naphthalene-2-acetate* (**18**) was obtained which was directly dissolved in MeOH (10 ml) and conc. aq. NaOH soln. (6 ml). After stirring for 20 h at r.t., the mixture was poured into 1N HCl (100 ml). The precipitate was filtered off and recrystallised from EtOH: 0.4 g (30%) of **19**. M.p. 152–155°. Anal. calc. for $C_{18}H_{20}Cl_2O_3$ (355.26): C 60.91, H 5.68, Cl 19.96, O 13.52; found: C 61.21, H 5.60, Cl 19.64, O 13.41.

N-Decylhydroxyl-amine (**25**). Overnight, 1-bromodecane (10 g), $NH_2OH \cdot HCl$ (12.5 g), and Et_3N (35 ml) were refluxed in EtOH (100 ml). After evaporation, the crude residue was diluted with H_2O (400 ml), the precipitate filtered off, washed with H_2O, dissolved in CH_2Cl_2/MeOH, and chromatographed on silica gel with CH_2Cl_2/MeOH 95:5: 4.7 g (39%) of **25**. The methanesulfonate of **25** was recrystallised from EtOH/Et_2O. M.p. 71–73°. Anal. calc. for $C_{11}H_{27}NO_4S$ (269.41): C 49.04, H 10.10, N 5.20, O 23.76, S 11.90; found: C 49.21, H 10.21, N 5.52, O 23.87, S 12.00.

Using procedures analogous to that for **25**, **26–31**, **33**, and **34** were prepared *(Table 8)*.

Table 8. *N-Alkylhydroxylamines* **25–31**, **33**, *and* **34** *Obtained from the Corresponding Bromoalkanes*

	R-Br	Base	Product	M.p. [°]	Yield [%]
25	$CH_3(CH_2)_9Br$	Et_3N	$CH_3(CH_2)_9NHOH$	71–73[a])	39
26	$CH_3(CH_2)_{10}Br$	Et_3N	$CH_3(CH_2)_{10}NHOH$	77–79[a])	25
27	$CH_3(CH_2)_{11}Br$	Et_3N	$CH_3(CH_2)_{11}NHOH$	76–77[a])	20
28	$CH_3(CH_2)_{12}Br$	Et_3N	$CH_3(CH_2)_{12}NHOH$	84–86[a])	21
29	$CH_3(CH_2)_{14}Br$	Et_3N	$CH_3(CH_2)_{14}NHOH$	88–90[a])	21
30	$CH_3(CH_2)_{10}Br$	Et_3N	$CH_3(CH_2)_{10}NH{-}OCH_3$	93–94[b])	48
31	$CH_3(CH_2)_{10}Br$	Et_3N	$CH_3(CH_2)_{10}N(OH)CH_3$	81–83[b])	42
33	$CH_3(CH_2)_{11}Br$	Et_3N	$CH_3(CH_2)_{11}N(OH)CH_3$	86–87[a])	76
34	$CH_3(CH_2)_{11}Br$	*N*-Methylmorpholine	$CH_3(CH_2)_{11}NHOCH_3$	87–88[b])	32

[a]) Methanesulfonate. [b]) Hydrochloride.

N,O-*Dimethyl*-N-*undecylhydroxylamine* (**32**). For 4 h, **30** (5 g) was refluxed together with HCOOH (22 ml) and paraformaldehyde (0.75 g). The mixture was poured into H_2O (500 ml) containing 30% NaOH soln. (5 ml) and extracted with Et_2O. The org. extract was dried ($MgSO_4$) and evaporated, and the crude residue triturated with EtOH/HCl to give 3.4 g (54%) of **32**·HCl which crystallised from EtOH/Et_2O. M.p. 103–105°. Anal. calc. for $C_{14}H_{30}ClNO$ (251.84): C 62.00, H 12.00, Cl 14.08, N 5.56, O 6.35; found: C 61.82, H 11.89, Cl 14.22, N 5.51, O 6.41.

Using an analogous procedure, N,O-*dimethyl*-N-*dodecylhydroxylamine hydrochloride* (**35**·HCl) was prepared in 77% yield. M.p. 101–103°. Anal. calc. for $C_{14}H_{32}ClNO$ (265.87): C 23.25, H 12.13, Cl 13.34, N 5.27, O 6.02; found: C 63.16, H 12.40, Cl 13.10, N 5.30, O 6.18.

4-(4-Propoxyphenyl)-3-buten-1-ol (**38**). Under Ar, {3-[(tetrahydro-2*H*-pyran-2-yl)oxy]propyl}triphenylphosphonium bromide (6.8 g) was suspended in Et_2O (80 ml) and K(*t*-BuO) (1.4 g) added. The suspension was stirred 45 min at r.t. and then 4-propoxybenzaldehyde (**36**; 2.3 g) in Et_2O (20 ml) added dropwise. The mixture was stirred for further 2 h, then H_2O (20 ml) added, and the Et_2O phase separated. The aq. phase was extracted 3 times with Et_2O, the combined extract washed with brine, dried ($MgSO_4$), and evaporated, and the residual crude oil chromatographed on silica gel with hexane/Et_2O 9:1 to give 1.8 g (44%) of the tetrahydropyranyl ether **37** as a colourless oil. Together with sat. HCl/EtOH (2.7 ml) in EtOH (30 ml), **37** was stirred at r.t. for 3 h. After evaporation, the residue was chromatographed on silica gel with hexane/Et_2O 1:1 to give 1 g (78%) of **38**. After recrystallisation from EtOH/EtOH, m.p. 41–43°. Anal. calc. for $C_{13}H_{18}O_2$ (206.28): C 75.69, H 8.79, O 15.51; found: C 75.42, H 8.94, O 15.65.

(E)-N-Methyl-N-[4-(4-propoxyphenyl)-3-butenyl]hydroxylamine (**41**). To **38** (0.5 g) in pyridine (5 ml), MsCl (1 ml) was added. The dark soln. was stirred at r.t. for 1½ h, then poured into H_2O (50 ml) and extracted with Et_2O. The extracts were washed with 0.1N HCl, dried ($MgSO_4$), and evaporated. Recrystallisation from Et_2O gave 0.6 g (88%) of the methanesulfonate (m.p. 38–40°) which was dissolved in MeOH (15 ml) and Et_3N (2 ml) and reacted with $NH_2OH \cdot HCl$ (0.7 g). The mixture was heated under reflux for 3 h. After cooling, the soln. was evaporated, the residue extracted with Et_2O, the Et_2O phase filtered and evaporated, and the crude oil purified by chromatography on silica gel with Et_2O/CH_2Cl_2 1:1. After reaction with HCl, **41**·HCl was obtained in 28% yield. M.p. 89–91°. Anal. calc. for $C_{14}H_{22}ClNO_2$ (271.79): C 61.91, H 8.16, Cl 13.05, N 5.20, O 11.77; found: C 61.72, H 7.94, Cl 12.92, N 5.20, O 11.84.

N-Methyl-N-[4-(4-propoxyphenyl)butyl]hydroxylamine (**40**) was prepared analogously in 44% yield. M.p. of **40**·HCl 110–112°. Anal. calc. for $C_{14}H_{24}ClNO_2$ (273.80): C 61.40, H 8.82, Cl 12.95, N 5.08, O 11.69; found: C 61.60, H 9.02, Cl 12.82, N 5.10, O 11.52.

4-(4-Propoxyphenyl)butan-1-ol (**39**). Under Ar, **38** (0.6 g) in EtOH (100 ml) was hydrogenated over 10% Pd/C (60 mg) at 50° and 5 atm for 6 h, then cooled, filtered, and evaporated: 0.5 g of **39** as colourless oil which was used without further purification.

7-Methylnaphthalen-2-ol. At 100°, 3,4-dihydro-7-methoxynaphthalen-1(2*H*)-one (28.8 g), formaldehyde (35%; 15.3 g), and benzylammonium chloride (24.7 g) were stirred for 2 h. After cooling to 40°, the mixture was poured into acetone (400 ml). The crystalline precipitate was filtered off, washed with acetone, and dried to give 38.4 g (71%) of *N-benzyl-(1,2,3,4-tetrahydro-7-methoxy-1-oxonaphthalene-2-methyl)amine*. M.p. 162–164°. To the latter in MeOH (250 ml), $NaBH_4$ (2.30 g) in H_2O (60 ml) containing 7 drops of 2N NaOH was added dropwise under cooling so that the temp. did not rise above 25°. The suspension was stirred for 2 h at r.t., then acidified to pH 4 with 20% HCl soln. (25 ml) within 15 min. The suspension was concentrated to 150 ml, diluted with H_2O (500 ml), brought to pH 9 with NaOH, and extracted with CH_2Cl_2 and the extract dried ($MgSO_4$) and evaporated to give 37.8 g (97.7%) of *N-benzyl-(1-hydroxy-1,2,3,4-tetrahydro-7-methoxynaphthalene-2-methyl)amine*. This yellow oil in HCl/EtOH (150 ml) was refluxed for 2 h, cooled, and diluted with EtOH (100 ml). On standing, 30 g (74.7%) of *N-benzyl-(3,4-dihydro-7-methoxynaphthalene-2-methyl)amine* crystallised. M.p. 205–208°. To these crystals in decalin (150 ml), 10% Pd/C (3 g) was added. The mixture was heated 20 h at 200°, then filtered, and the solvent distilled off under reduced pressure. The residue was sublimed to give 12.1 g (65.2%) of *2-methoxy-7-methylnaphthalene* as white crystals. M.p. 84–87°. To this compound in CH_2Cl_2 (100 ml) at −10°, BBr_3 (21.8 g) was added within 20 min. The mixture was stirred for 2 h at −10°, then poured into H_2O (100 ml)/ice, the org. layer separated, and the aq. phase extracted with CH_2Cl_2. The combined org. phase was dried ($MgSO_4$) and evaporated to give 6.5 g (94.3%) of *7-methylnaphthalen-2-ol*. M.p. 113–115°, after recrystallisation from Et_2O/hexane. Anal. calc. for $C_{11}H_{10}O$ (158.20): C 83.51, H 6.37, O 10.11; found: C 83.61, H 6.20, O 10.32.

N-Methyl-N-(7-propoxynaphthalene-2-methyl)hydroxylamine (**44**). For 16 h, 7-methylnaphthalen-2-ol (3.2 g) was stirred under reflux together with 1-bromopropane (5 g), diisopropyl ketone (30 ml), HMPA (3 ml), and K_2CO_3 (5.6 g). After filtration and washing with acetone, the soln. was evaporated, the residue dissolved in Et_2O, the soln. washed with NaOH soln. and brine, dried ($MgSO_4$), and evaporated. The crude product was chromatographed on silica gel with hexane/Et_2O 9:1: 3.3 g (81.5%) of *2-methyl-7-propoxynaphthalene* (**42**). M.p. 50–53°, after crystallisation from Et_2O. Under Ar and UV irradiation, **42** was heated for 16 h with freshly crystallised *N*-bromosuccinimide (2.94 g), dibenzoylperoxide (10 mg), and K_2CO_3 (0.23 g) in CCl_4 (100 ml). After cooling, the mixture was filtered, mixed with silica gel and chromatographed on silica gel with hexane/Et_2O 9:1 to give 2.5 g (55%) of *2-(bromomethyl)-7-propoxynaphthalene* (**43**; m.p. 94–96° from Et_2O/hexane). To **43** in EtOH (75 ml), $NH_2OH \cdot HCl$ (3 g) and Et_3N (7.5 ml) were added. The mixture was heated under reflux for 16 h, the solvent removed, and the crude residue washed with Et_2O and filtered. The Et_2O extract was concentrated and diluted with hexane: 1.3 g (59%) of crystalline **44** were filtered off. M.p. 106–108°. Anal. calc. for $C_{15}H_{19}NO_2$ (245.32): C 73.42, H 7.78, N 5.74, O 12.92; found: C 73.14, H 7.92, N 5.70, O 13.20.

Using an analogous procedure, **54** and **55** were prepared.

N-(7-Butoxynaphthalene-2-methyl)-N-methylhydroxylamine (**54**). M.p. 90–91°. Anal. calc. for $C_{16}H_{21}NO_2$ (259.35): C 74.10, H 8.17, N 5.36, O 12.32; found: C 74.10, H 8.22, N 5.41, O 12.38.

*N-Methyl-N-(7-Pentoxynaphthalene-2-methyl)-*hydroxylamine (**55**). M.p. 68–71°. Anal. calc. for $C_{17}H_{23}NO_2$ (273.38): C 74.72, H 8.48, N 5.12, O 11.73; found: C 74.59, H 8.62, N 5.31, O 11.82.

2-[N-Hydroxy-N-(7-propoxynaphthalene-2-ethyl)amino]acetohydrazide (**59**). For 4 h, *N-(7-propoxynaphthalene-2-ethyl)hydroxylamine* (0.5 g) was stirred together with ethyl bromoacetate (0.33 g), Et_3N (2 ml), and 3,4,5,6-tetrahydro-1,3-dimethyl-2(1*H*)-pyrimidinone (1 ml) in THF (10 ml) at r.t. The white suspension was evaporated, the residue partitioned in Et_2O/H_2O and extracted with Et_2O, and the combined org. extract dried ($MgSO_4$) and evaporated. The remaining crude oil was chromatographed on silica gel with Et_2O/CH_2Cl_2 1:1 to

give 0.6 g (91%) of *ethyl 2-[N-hydroxy-N-(7-propoxynaphthalene-2-ethyl)amino]acetate* as a waxy solid which was heated under reflux together with $NH_2NH_2 \cdot H_2O$ (0.21 g) in EtOH (1.5 ml) for 5 min. The precipitate was filtered off, washed with EtOH and Et_2O to yield 0.4 g (70%) of **59**. M.p. 168–170°. Anal. calc. for $C_{17}H_{23}N_3O_3$ (317.39): C 64.32, H 7.28, N 13.24, O 15.18; found: C 64.62, H 7.31, N 13.32, O 15.02.

Using an analogous procedure, **60** and **61** were prepared.

4-[N-Hydroxy-N-(7-propoxynaphthalene-2-ethyl)amino]butanohydrazide (**60**). M.p. 136–138°. Anal. calc. for $C_{19}H_{27}N_3O_3$ (345.45): C 66.12, H 7.92, N 12.18, O 12.85; found: C 65.87, H 8.02, N 11.94, O 13.96.

6-[N-Hydroxy-N-(7-propoxynaphthalene-2-ethyl)amino]hydrazide (**61**). M.p. 130–131°. Anal. calc. for $C_{21}H_{31}N_3O_3$ (373.52): C 67.52, H 8.38, N 11.29, O 12.85; found: C 67.20, H 8.41, N 11.02, O 12.63.

Sodium 6-[N-Hydroxy-N-(7-propoxynaphthalene-2-ethyl)amino]hexanoate (**62**). For 1 h, *methyl 6-[N-hydroxy-N-(7-propoxynaphthalene-2-ethyl)amino]hexanoate* (2 g) was refluxed with 5N NaOH (22 ml). The crystals were filtered off, washed with ice/H_2O and dried to give 0.7 g (34%) of **62**. M.p. 222–224° (dec.). Anal. calc. for $C_{21}H_{28}NNaO_4$ (381.45): C 66.12, H 7.43, N 3.68, Na 5.92, O 16.83; found: C 65.93, H 7.32, N 3.59, O 16.88.

7-Propoxynaphthalene-2-carbaldehyde (**66**). To a soln. of *ethyl 7-propoxynaphthalene-2-acetate* (**45**) in dioxan (150 ml), sand (1 g) and SeO_2 (8.2 g) were added. The mixture was stirred at 100° for 2 days, then filtered, and evaporated. The crude product was chromatographed on silica gel with Et_2O/hexane 4:1 to 1:1 to give 15 g (71%) of *ethyl α-oxo-7-propoxynaphthalene-2-acetate* (**65**) as an oil. Its soln. in 2N NaOH (140 ml) was stirred for 2 h at r.t. Then H_2O (1 l) was added, the mixture extracted with Et_2O, and the Et_2O extract dried ($MgSO_4$) and evaporated to give 8 g of **65**. The aq. phase was acidified with HCl to pH 3 and extracted with CH_2Cl_2 to give 6.1 g of α-oxo-7-propoxynaphthalene-2-acetic acid. M.p. 105–107°. The recovered **65** was again dissolved in 2N NaOH and, after boiling for 30 min, worked up as described above. Altogether, 12.7 g of yellow crystalline α-oxo-7-propoxynaphthalene-2-acetic acid were obtained which was powdered and mixed with aniline (5.8 g), heated 2 h at 100° (until foaming ceased), diluted with 25% H_2SO_4 soln., and heated for another 15 min at 100°. After cooling, H_2O (300 ml) was added and the soln. extracted with CH_2Cl_2. The org. extracts were dried and evaporated to give 9.7 g of a dark residue which was chromatographed on silica gel with hexane/Et_2O 4:1 to yield 8.6 g (76%) of **66**. M.p. 57–59°, after crystallisation from Et_2O/hexane. Anal. calc. for $C_{14}H_{14}O_2$ (214.26): C 78.48, H 6.58, O 14.93; found: C 78.30, H 6.62, O 15.03.

2-Nitro-1-(7-propoxy-2-naphthalenyl)-1-propene (**67**). At 100°, **66** (9.4 g) was heated with NH_4OAc (3.9 g) in nitroethane (50 ml) for 5 h. After cooling, CH_2Cl_2 (100 ml) was added, the soln. washed with H_2O, dried, and evaporated. The residual clear brown oil was chromatographed on silica gel with hexane/Et_2O 4:1 to give 7.1 g (59.6%) of **67** as yellow crystals from Et_2O/hexane. M.p. 67–69°. Anal. calc. for $C_{16}H_{17}NO_3$ (271.37): C 70.82, H 6.34, N 5.16, O 17.68; found: C 70.68, H 6.56, N 5.32, O 17.84.

Methyl (7-Propoxynaphthalene-2-methyl) Ketone. To a suspension of **67** (7 g) in EtOH (200 ml) at 60°, *Raney* Ni (4.4 g) and a soln. of sodium phosphite (25.8 g) in H_2O (100 ml) and 1N HCl (129 ml) were added simultaneously in small portions. The grey suspension was stirred for further 2 h at 60°, then cooled to 30° and filtered. The pink soln. was diluted with H_2O (300 ml) and the resulting precipitate filtered off to yield 5.6 g (89.6%) of the title compound as a pink crystalline solid. M.p. 54–56°. Anal. calc. for $C_{16}H_{18}O_2$ (242.30): C 79.31, H 7.48, O 13.20; found: C 79.43, H 7.56, O 13.35.

N-Methyl-N-(α-methyl-7-propoxynaphthalene-2-ethyl)hydroxylamine (**64**). To a soln. of methyl (7-propoxynaphthalene-2-methyl) ketone (5.5 g) in EtOH (150 ml) was added dropwise during 30 min a soln. of $NaBH_4$ (0.43 g) in H_2O (20 ml) containing 2 drops of NaOH soln. and the mixture was stirred at r.t. for 1 h. Then, 20% H_2SO_4 soln. (20 ml) was added, the mixture stirred for further 30 min at r.t., diluted with H_2O (800 ml), and extracted with CH_2Cl_2. After drying and filtration, the org. phase was concentrated to yield 5.3 g (95.6%) of *1-(7-propoxynaphthalen-2-yl)-2-propanol* (**68**) which crystallised from Et_2O as a pale pink powder. M.p. 78–81°. As described for **2**, **68** was converted to **64** in 35% yield *via* its methanesulfonate. M.p. 93–95°. Anal. calc. for $C_{17}H_{23}NO_2$ (273.33): C 74.70, H 8.47, N 5.13, O 11.70; found: C 74.91, H 8.60, N 5.10, O 11.82.

10-Propoxynaphth[1,2-d]azepin-3-ol (**74**). For 6 days, *ethyl 7-propoxynaphthalene-1-acetate* (**69**; 26 g) was heated under reflux with dioxan (180 ml), sand (1 g), and SeO_2 (10.6 g), then filtered, and evaporated. After chromatography on silica gel with hexane/Et_2O 3:1, 17.7 g (64.7%) of *ethyl α-oxo-7-propoxynaphthalene-1-acetate* (**70**) were obtained as a brown oil. To a soln. of **70** in MeOH (200 ml), a soln. of $NaBH_4$ (1.1 g) in H_2O (25 ml) containing 10 drops of conc. aq. NaOH soln. was added dropwise during 10 min at r.t. The mixture was stirred for 15 min, then acidified to pH 4 with H_2SO_4, poured into H_2O (1 l) and extracted with CH_2Cl_2. The extract was dried and evaporated and the crude product chromatographed on silica gel with hexane/Et_2O 1:1 to yield 11.9 g (73%) of ethyl *α-hydroxy-7-propoxynaphthalene-1-acetate* (**71**) as an oil, which was heated together with triethyl orthoacetate (56 g) and hexanoic acid (0.5 g) under reflux for 6 h under Ar at 200°. Through the attached *Vigreux* column, 1.2 ml of a colourless liquid were distilled over. The column was then removed and the mixture kept at 185°

for 6 h. After evaporation, the crude product was chromatographed on silica gel with hexane/Et_2O 1:1 yielding 4.5 g (31%) of *diethyl 7-propoxynaphthalene-1,2-diacetate* (**72**) as an oil, which was dissolved in dry THF (180 ml) and added to a suspension of $LiAlH_4$ (0.72 g) in THF (100 ml) during 10 min. The mixture was stirred for further 30 min at r.t. and then H_2O (2 ml) was added dropwise. The mixture was again stirred for 30 min, filtered, and evaporated. The product was chromatographed on silica gel with Et_2O/CH_2Cl_2 1:1 to give 2.7 g (78%) of *7-propoxynaphthalene-1,2-diethanol* (**73**) as an oil. To a soln. of **73** in pyridine (50 ml) at 0°, MsCl (4.5 ml) was added. The mixture was stirred at 0° for 30 min, then poured into H_2O and extracted with Et_2O. The Et_2O extract was dried ($MgSO_4$) and evaporated. The crude dimesylate was refluxed together with Et_3N (4.5 ml) and $NH_2OH \cdot HCl$ (360 mg) in EtOH (50 ml) for 1 h, then more $NH_2OH \cdot HCl$ (150 mg) was added and the mixture refluxed for another 30 min. The solvent was evaporated and the residue dissolved in CH_2Cl_2, washed with H_2O, dried, and evaporated. After chromatography on silica gel with Et_2O/CH_2Cl_2 1:1, **74** (1 g, 37%) was isolated as grey powder. M.p. 146–148° (from Et_2O). Anal. calc. for $C_{17}H_{21}NO_2$ (271.36): C 75.20, H 7.81, N 5.24, O 11.79; found: C 74.93, H 8.11, N 5.13, O 11.60.

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