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Determination of the chemical structure of potential organic impurities occurring in the drug substance opipramol

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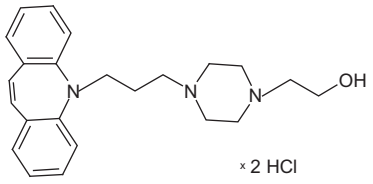
The tricyclic antipsychotic and antidepressant drug opipramol (opipramole) was examined with regard to the chemical structure of its organic impurities. Impurities were isolated from the technical product by chromatographic methods and their chemical structures were established by ^{1}H NMR, MS and FTIR and further confirmed by comparison with commercially available products or with products obtained by independent synthesis, and in one case additionally by X-ray structure analysis.

1. Introduction

The purity of chemical products is of the highest importance, especially for pharmaceuticals. For human drugs, in most cases the maximum concentration of an individual impurity is determined by the respective Pharmacopoeia or ICH regulations; the highest permissible level of the total impurities is not more than 0.5%. However, some impurities may accumulate in an organism; they may be toxic, carcinogenic or may possess other dangerous properties. Therefore it is important to know more about their chemical nature.

Opipramol, 2-[4-(3-dibenzo[b,f]azepin-5-yl-propyl)-piperazin-1-yl]-ethanol dihydrochloride, was chosen for study, as its impurities have not yet been described in detail. We present details concerning the isolation and structure determination of the impurities.



Opipramol dihydrochloride

Opipramol is obtained by a set of reactions comprising alkylation, typically with 1-bromo-3-chloropropane, of iminostilbene (dibenzoazepine) and condensation of the intermediate *N*-(halopropyl)iminostilbene with *N*-(2-hydroxyethyl)piperazine (Scheme 1).

According to the original Geigy patents (Schindles 1957, 1962) the first step requires the use of a strong base such as sodium amide in a non-aqueous medium to convert iminostilbene into its anion, which is subsequently *N*-alkylated. Due to the inconvenience of using sodium amide and the formation of by-products, modifications of iminostilbene alkylation were developed. Thus, alkylation of iminostilbene was carried out at room temperature in a two-phase system in the presence of aqueous sodium hydroxide or solid potassium hydroxide and a phase transfer catalyst (Gozlan et al. 1982). However, formation of side products was also observed in these syntheses. One of the impurities formed in both cases is *N*-allyliminostilbene, which dominates if iminostilbene reacts with 1-bromo-3-chloropropane in the presence of solid potassium hydroxide (Gozlan et al. 1982).

N-(3-Halopropyl)dibenzoazepine may also be obtained in the reaction of iminostilbene with an excess of 1-bromo-3-chloropropane in the presence of a weak base (Na_2HPO_4, K_2HPO_4; or alkali, alkaline earth or ammonium acetate) and a phase transfer agent (Breviglieri et al. 2004). The mixture of *N*-(bromopropyl)iminostilbene and *N*-(chloropropyl)iminostilbene formed was reacted with *N*-(2-hydroxyethyl)piperazine in the presence of a weak base to give opipramol. The reactions are carried out in toluene.

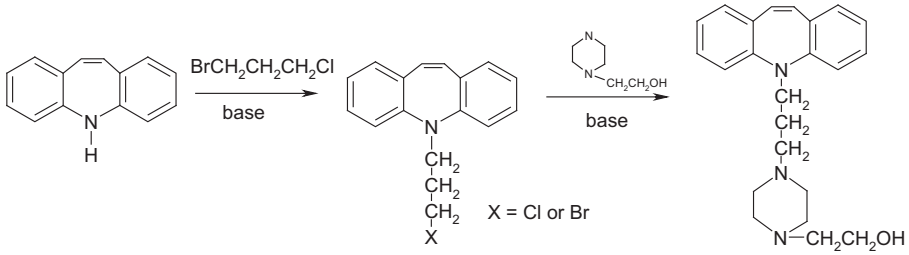
According to a European patent (Gutman and Ashkar 1994, 1995) *N*-(3-halopropyl)iminostilbene is obtained *via* alkylation of iminostilbene with 1-bromo-3-chloropropane in the presence of potassium carbonate, a small amount of polyethylene glycol 6000 and a small amount of water. The *N*-(3-halopropyl)iminostilbene was in turn reacted with *N*-(2-hydroxyethyl)piperazine in the absence of another base to form opipramol.

In all of the above procedures the opipramol base formed is finally converted into dihydrochloride.

Considering the chemistry of opipramol synthesis, various byproducts could be anticipated as potential impurities. Some of these impurities, particularly the less polar ones, were isolated from technical lots and identified.

2. Investigation, results and discussion

The potential impurities of opipramol isolated from toluene preconcentrate are shown in Fig. 1 Structures of these compounds were at first solved tentatively by spectroscopic methods and then confirmed by comparison with commercially available products, or with the respective standards obtained by independent synthesis or by X-ray studies.



Scheme 1: Synthesis of opipramol

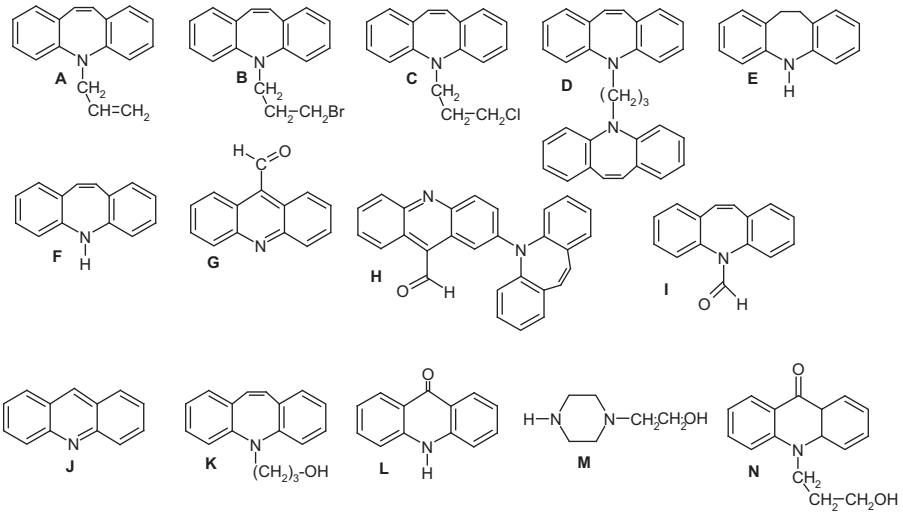


Fig. 1: Identified impurities of opipramol isolated from technical product

Impurities of the opipramol drug substance may be of different origins; compounds **F** and **M** are starting materials whereas compounds **B** and **C** are intermediates in the synthesis. Compound **D** is formed by reaction of dibenzoazepine with the bromopropyl intermediate rather then with chloropropyldibenzoazepine. Hydroxypropyldibenzoazepine **K** is the hydrolysis product of **B** or **C** under strongly alkaline conditions. The allyldibenzoazepine **A** forms under similar conditions from the intermediates **B** or **C** as an elimination product (Gozlan et al. 1982). To decrease the formation of this side product much milder reactions conditions were developed (Farchemia, Patent 2004; Tharo Pharmaceutical Industries, Patent 1994). It was also found that the starting material dibenzoazepine **F** is contaminated by dihydrobenzoazepine **E**. Compounds **G**, **H**, **I**, **J**, **L** and **N** are oxidation/rearrangement products of dibenzoazepine (or *N*-substituted dibenzoazepine). Such reactions are described in the literature, for example (Belluci et al. 1987; Ohta et al. 1981; Cann et al. 1988; Clayton et al. 1998).

Synthetic routes to compounds **A**, **B**, **C**, **D**, **G**, **H**, **I**, **J**, **K**, and **N** are shown in Scheme 2.

Route **III** (reactions 3.2.3 – see Experimental) was performed to establish the influence of the conditions of coupling dibenzoazepine with bromochloropropane on the yield and proportion of 3-chloropropyldibenzoazepine and 3-bromopropyldibenzoazepine, the intermediates in opipramol synthesis. The highest yield of compound **C** was achieved in reaction performed in ethanol, in the presence of a phase transfer catalyst and sodium carbonate as a base.

Compound **N** was obtained by acridone alkylation, but it could be also prepared by oxidation of hydroxypropyldibenzoazepine **K** with yield 12% as described by Ohta et al. (1981).

Red compound **H** to the best of our knowledge has not been described in particular as a product of iminostilbene oxidation. It is also a byproduct in opipramol synthesis. Furthermore, its formation has been observed in dibenzoazepine alkylation reactions, especially if the alkylation is performed as described the literature (Gozlan et al. 1982). It is formed in relatively high quantities if dibenzoazepine is treated with PCC (red, unstable iminostilbene oxidation product, with Fremy's salt as oxidizer, was described (Rosowsky et al. 2004), and is in fact dibenzo[*b*,*f*]azepin-2-one). The structure of compound **H** (Fig. 2) was confirmed by X-ray analysis. Crystallographic data and refinement parameters for the compound are given in Table 1.

Compound **H** is deep red with characteristic red fluorescence. Absorption and emission spectra of **H** are shown in Fig. 3.

Compound **I** is also a byproduct in opipramol synthesis. To our knowledge it has not been described as a product of iminostilbene oxidation. Probably the formyl group is transferred from acridine-9-carbaldehyde to the iminostilbene nitrogen atom.

Potential impurities of opipramol may be detected and identified by simple TLC with the use of selected chromatographic systems; R_f values for opipramol and its impurities are listed in Table 2.

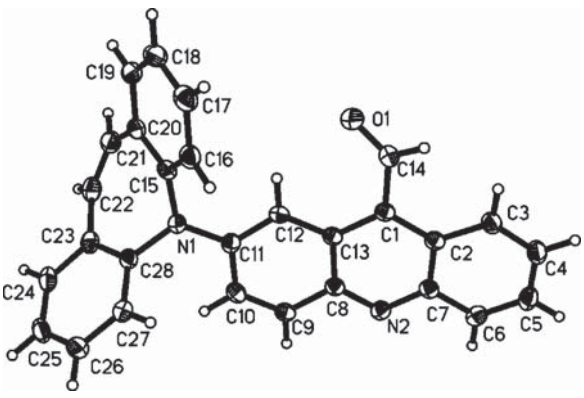
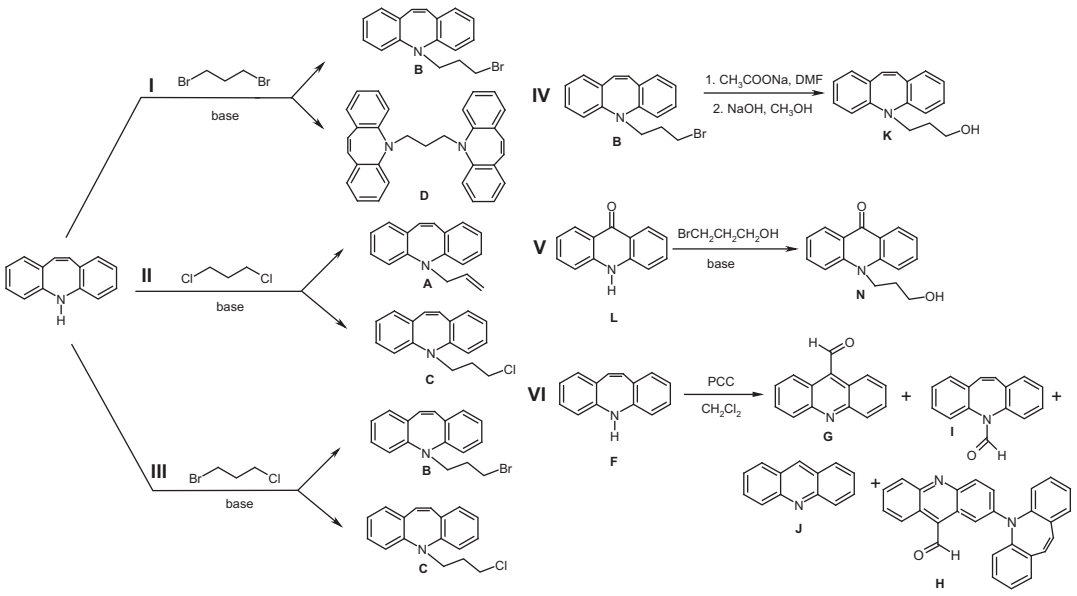


Fig. 2: Crystal structure of compound **H**



Scheme 2: Synthetic routes to impurities of opipramol

Table 1: Crystal data and structure refinement for compound H

Empirical formula	$C_{28}\ H_{18}\ N_2\ O$	
Formula weight	398.44	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	monoclinic	
Space group	$P\ 2_1/n$	
Unit cell dimensions	a = 8.1529(7) Å	α = 90°.
	b = 13.0625(14) Å	β = 96.251(10)°.
	c = 18.119(2) Å	γ = 90°.
Volume	1918.2(3) Å^3	
Z	4	
Density (calculated)	1.380 Mg/m^3	
Absorption coefficient	0.084 mm^{-1}	
F(000)	832	
Crystal size	0.22 × 0.16 × 0.08 mm^3	
Theta range for data collection	2.26 to 25.50°.	
Index ranges	−9 <= h <= 9, −15 <= k <= 15, −21 <= l <= 21	
Reflections collected	10973	
Independent reflections	3389 [R(int) = 0.0427]	
Completeness to theta = 25.50°	95.1%	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3389 / 0 / 280	
Goodness-of-fit on F^2	1.003	
Final R indices [I>2sigma(I)]	R1 = 0.0517, wR2 = 0.1342	
R indices (all data)	R1 = 0.0781, wR2 = 0.1439	
Largest diff. peak and hole	0.449 and −0.226 e.Å^{-3}	

Table 2: R_f values for opipramol base (OB) and impurities of technical opipramol in different solvent systems as mobile phases

	A	B	C	D	E	F	G	H	I	J	K	L	OB	M	N
[a]	0.99	0.99	0.99	0.98	0.95	0.90	0.88	0.89	0.90	0.78	0.75	0.72	0.50	0.35	0.28
[b]	0.96	0.95	0.95	0.93	0.90	0.88	0.86	0.87	0.86	0.80	0.75	0.68	0.40	0.35	0.25
[c]	0.97	0.95	0.93	0.90	0.71	0.56	0.28	0.25	0.10	0.25	0.23	0.20	0.12	0.11	0.10

[a] chloroform-methanol (5:2);
[b] chloroform-methanol (19:1);
[c] hexane-methylene chloride (1:1)

Table 3: HPLC retention times of opipramol dihydrochloride (OP) and impurities of technical opipramol

Compound	A	B	C	D	F	G	H	J	K	L	M	N	OP
Retention time[a] (min)	–	–	–	–	10.88	6.56	–	7.38	6.86	2.81	2.73	2.40	6.03
Retention time[b] (min)	2.19	2.31	2.32	3.28	1.98	–	3.63	–	–	–	–	–	–

[a] Mobile phase: acetonitrile-buffer (55:45);
[b] mobile phase: acetonitrile

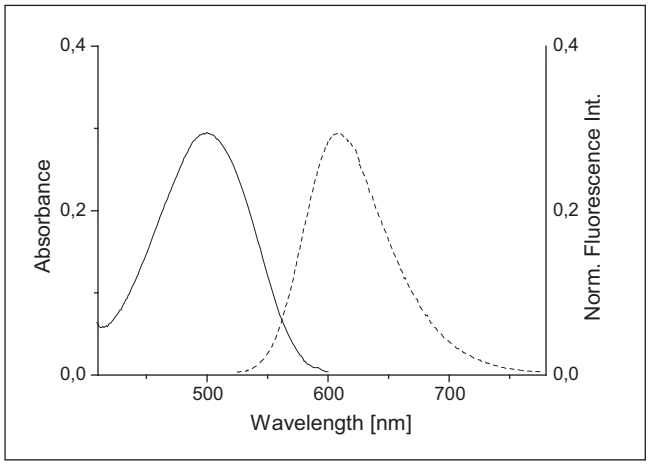


Fig. 3: Absorption (solid line) and fluorescence (dashed line) spectra of compound **H** in acetonitrile

The impurities were also subjected to HPLC analysis. The aim of this procedure was to establish the retention behavior of the impurities in relation to the main drug component, opipramol. Selected impurities and opipramol were chromatographed in two different mobile phases: acetonitrile-buffer (55:45) and pure acetonitrile (Table 3).

As can be seen, most of the compounds investigated are easily resolvable by HPLC. Only compounds **B** and **C**, are not fully separated due to similar retention times.

In conclusion, our results could indicate what kind of compounds should be considered for analysis as substances that could be present as impurities of the pharmaceutical product opipramol. Besides the obvious impurities as substrates and intermediates we pay attention to products of intermediate(s) hydrolysis and, in particular to widely analyzed oxidation products e.g. in the case of carbamazepine and opipramol in particular. The formation of compound **H** is rather unexpected. Its intense red color may contribute to the color of the pharmaceutical product. Formation of compound **I** on oxidation of iminostilbene residue has also not been published. The technical opipramol used in this study was exhaustively purified and the purified drug substance contains not more than 0.05% of iminostilbene, not more than 0.10% of any other impurity and the sum of total impurities is not more than 0.5%, thus it fulfills ICH requirements. However, there is a need to know more about possible impurities due to their potential dangerous properties. Such information may also be useful for quality control units of pharmaceutical plants.

Due to the availability of standards, compounds that are potential impurities of opipramol may be characterized by REAL absorption coefficients, hence enabling determination of their REAL concentration in opipramol substance.

3. Experimental

All chemicals and reagents were of the highest purity commercially available. The standards, opipramol base, its dihydrochloride, iminostilbene **F**, compound **E** (10,11-dihydro-5*H*-dibenzo[*b,f*]azepine) and compound **M** (2-hydroxyethylpiperazine), were supplied by Pharmaceutical Works POLPHARMA S.A. (Starogard Gdański). Acridine (compound J) and 9(10*H*)-acridone (compound L) were purchased from Sigma–Aldrich. Other impurities isolated were compared with synthesised compounds obtained by suitable procedures. Silica gel 60 (63–200 μm) for column chromatography and aluminium sheets covered with silica gel $60F_{254}$ for TLC were from Merck. In TLC, after developing, the separated compounds were visualized by UV at 254 and 365 nm or by exposing to iodine vapors. The mobile phases were mainly mixtures of chloroform and methanol, methylene chloride and acetone, or hexane and methylene chloride in different proportions. All solvents were of analytical grade.

The HPLC system consisted of a NUCLEODUR 100-5C18ec Macharey-Nagel column (150 × 4.6 mm, particle size 5 μm), Merck-Hitachi Intelligent Pump (model L-6200), UV-VIS detector (model L-4250) and Chromato-Integrator (D-2500).

^{1}H NMR: Spectra were recorded on a Varian instrument at 500 MHz in $CDCl_3$. The chemical shift of the residual solvent signal served as internal standard. FTIR: Spectra were recorded on a Mattson Genesis II Instrument. MS: Mass spectra were taken on an AMD-604 apparatus.

3.1. Isolation of impurities

The opipramol substance produced by POLPHARMA S.A. fulfils ICH requirements; it is very pure and isolation of impurities in quantities required for unequivocal identification was troublesome. For that reason, the more highly contaminated crude technical product was chosen as a source of byproducts. The crude material was extracted using different solvents; enrichment of impurities was evaluated and particular compounds were localized on TLC plates. Finally, toluene was chosen to obtain solutions containing the impurities in a suitable ratio to the main component. The toluene extracts were preconcentrated, the excess opipramol deposited was removed by filtration and components of the residual solution were separated by preparative thin layer chromatography. Silica gel portions containing particular impurities were collected from the chromatographic plate(s) and extracted with methylene chloride, methanol or their mixtures. The solutions of separated impurities were ultimately rechromatographed and subjected to spectral analysis. Chemical structures of isolated compounds (Fig. 1) were proposed on the basis of ^{1}H NMR, FTIR and MS analysis.

3.2. Syntheses

*3.2.1. Synthesis of compounds **B** and **D**. Iminostilbene reactions with 1,3-dibromopropane*

A mixture of iminostilbene (2.00 g, 10.4 mmol), 1,3-dibromopropane (1.50 mL, 14.8 mmol), and K_2CO_3 (6.12 g, 44.3 mmol) in DMF (15 mL) was stirred and maintained at 80 °C for 20 h. The mixture was diluted with water and extracted with ethyl acetate. Compound **D** was isolated from the extract by column chromatography using hexane-methylene chloride (1:1) mixture. Yield 28%.

A mixture of iminostilbene (2.00 g, 10.4 mmol), 1,3-dibromopropane (4.00 mL, 40 mmol), tetra-*n*-butylammonium iodide (0.40 g), 50% NaOH (11 mL), and toluene (12 mL) was heated at 85 °C for 4 h with vigorous stirring. The toluene layer was separated and washed four times with water. After drying with $MgSO_4$ the solvent was evaporated under reduced pressure. Compound **B** 1.57 g (48%) was isolated by column chromatography using hexane-methylene chloride (3:1) mixture as eluent.

*3.2.2. Synthesis of compounds **A** and **C**. Iminostilbene reaction with 1,3-dichloropropane*

A mixture of iminostilbene (2.50 g, 13 mmol), 1,3-dichloropropane (3.8 mL, 44 mmol), K_2CO_3 (10.75 g, 78 mmol), tetra-*n*-butylammonium iodide (0.5 g) and DMF (20 mL) was maintained at 100 °C for 15 h with stirring. The reaction mixture was diluted with water, and the solid deposited was collected and separated by column chromatography using methylene chloride-hexane (1:3) mixture as eluent. From the fraction containing **A** and **C,** the pure compounds were isolated by preparative TLC using a toluene-ethyl acetate-hexane (1:1:8) mixture as a mobile phase. Yield: 14% **A**, 11% **C**.

Table 4: Reaction conditions and ratio of compounds B and C in reactions 3.2.3 a-c

Reaction	Temp. [°C]	Time [h]	Yield [%]	%**B**; %**C** [mol/mol]
a	80	6	43	43; 57
b	50	24	40	25; 75
c	rt	48	25	10; 85

*3.2.3. Synthesis of compounds **B** and **C**. Iminostilbene reactions with 1-bromo-3-chloropropane*

a-c) A stirred mixture of iminostilbene (2.50 g, 13 mmol), 1,3-bromochloropropane (5.3 mL, 50 mmol), K_2CO_3 (11 g, 79 mmol) and tetra-*n*-butylammonium iodide (0.5 g) in DMF (11 mL), was reacted under conditions given in Table 4. The mixture was diluted with water and extracted with ethyl acetate. The products separated by column chromatography using methylene chloride-hexane (1:3) gave a mixture of compounds **B** and **C** in different ratios (see Table 4).

d) A mixture of iminostilbene (2.50 g, 13 mmol), 1,3-bromochloropropane (5.3 mL, 50 mmol), Na_2CO_3 (5.3 g, 50 mmol) and tetra-*n*-butylammonium iodide (0.75 g) in ethanol (25 mL) was stirred under reflux for 4 h. To the cooled mixture methylene chloride (50 mL) was added. The deposit was separated, washed with methylene chloride and discarded. The filtrate was concentrated and separated on a column using methylene chloride-hexane (1:3) mixture. Yield 1.42 g (40%) of a product consisting of >90% **C** and < 10% **B**.

*3.2.4. Synthesis of N-(3-hydroxypropyl)-5H-dibenzo[b,f]azepine, compound **K***

A mixture of 5-(3-bromopropyl)-5*H*-dibenzo[*b,f*]azepine (compound **B**) (1.20 g) and sodium acetate (0.45 g) in DMF (15 mL) was heated at 120 °C overnight. The mixture was diluted with water and extracted with hexane-ethyl acetate (4:1) mixture. The solvent was evaporated and the residue was hydrolyzed with 5 mL conc. NaOH solution in methanol. After 2.5 h the mixture was diluted with water and extracted with chloroform. After evaporation of the solvent, the residue was purified by column chromatography using hexane-methylene chloride (3:1), (1:1) and finally with methylene chloride as eluent. It was obtained 0.62 g (65%) of compound **K**.

*3.2.5. Synthesis of N-(3-hydroxypropyl)-9(10H)-acridone, compound **N***

A mixture of 9(*10H*)-acridone (0.70 g, 3.6 mmol), 3-bromo-1-propanol (0.33 mL, 3.6 mmol), K_2CO_3 (0.5 g, 3.6 mmol) and DMF (15 mL) was stirred at 60 °C for 4 h and the reaction mixture was then diluted with water. The solid was collected by filtration and washed with chloroform. The organic solution was evaporated and the residue was purified by preparative TLC using chloroform-methanol (20:1) mixture. Yield 24% of compound **N**.

*3.2.6. Synthesis of compounds **G**, **H**, **I** and **J** by oxidation of iminostilbene with PCC*

To pyridinium chlorochromate (PCC) (10.0 g) in methylene chloride (50 mL), an iminostilbene suspension (4.8 g, 25 mmol) in methylene chloride (50 mL) was added in portions. The mixture was stirred at room temperature for 24 h. The reaction mixture was filtered through an aluminium oxide layer under vacuum and the filter bed was washed with methylene chloride until the filtrate was colorless. The concentrated filtrate was chromatographed as soon as possible by preparative TLC using dichloromethane. Yield: 15% **G,** 13% **I**, 12% **J** and 4% **H**.

3.3. Characteristics of potential impurities of opipramol (mainly for those not commercially available or not fully characterized in the literature)

*Compound **A***: 5-Allyl-5*H*-dibenzo[*b,f*]azepine; m.p. 29–30 °C (lit. 40–42 °C (Sadashiva et al. 2005)); ^{1}H NMR: δ = 7.27 (t, *J* = 7.6 Hz, 2H), 7.10 (dd, J_1 = 7.3 Hz, J_2 = 1.4 Hz, 2H), 6.99–7.03 (m, 4H), 6.79 (s, 2H), 5.87–5.78 (m, 1H), 5.34 (dd, J_1 = 17.1 Hz, J_2 = 1.5 Hz, 1H), 5.14 (dd, J_1 = 10.4, J_2 = 1.5 Hz, 1H), 4.45 (d, *J* = 5.4 Hz, 2H). FTIR (film) ν = 3071, 3018, 2979, 2838, 1643, 1593, 1572, 1484, 1458, 1437, 1414, 1355, 1298, 1234, 1117, 1051, 984, 919, 789, 715, 644 cm^{-1}.

*Compound **B***: 5-(3-Bromopropyl)-*5H*-dibenzo[*b,f*]azepine; m.p. 77–78.5 °C (crystallized from methanol at low temperature); ^{1}H NMR: δ = 7.35–7.31 (m, 2H), 7.14 (dd, J_1 = 7.3 Hz, J_2 = 1.5 Hz, 2H), 7.09–7.05 (m, 4H), 6.81 (s, 2H), 3.94 (t, *J* = 6.4 Hz, 2H), 3.54 (t, *J* = 6.8 Hz, 2H), 2.13 (quintet, *J* = 6.4 Hz, 2H), MS (EI): found *m/z* = 314 and 316 (intensity 1:0.9) [M$^+$], for $C_{17}H_{16}NBr$ calcd. 315. FTIR (film) ν = 3019, 2960, 2850, 1592, 1570, 1435, 1238, 1115, 790, 761 cm^{-1}.

*Compound **C***: 5-(3-Chloropropyl)-*5H*-dibenzo[*b,f*]azepine; m.p. 63.5–65 °C (methanol at low temperature) (lit. 67 °C (Geigy, Patent 1962)); ^{1}H NMR: δ = 7.29–7.26 (m, 2H), 7.09–7.07 (m, 2H), 7.05–6.99 (m, 4H), 6.74 (s, 2H), 3.90 (t, *J* = 6.35 Hz, 2H), 3.63 (t, *J* = 6.3 Hz, 2H), 2.01 (quintet, *J* = 6.4 Hz, 2H), MS (EI): found *m/z* = 269 and 271 (intensity 1:0.3) [M$^+$], for $C_{17}H_{16}NCl$ calcd. 269.5. FTIR (film) ν = 2954, 2922, 2850, 1592, 1484, 1460, 1436, 1297, 1239, 1115, 1046, 789, 763 cm^{-1}.

*Compound **D***: 1,3-Bis(5*H*-dibenzo[*b,f*]-azepin-5-yl)-propane; m.p.164–166 °C (2-propanol) (lit. 163–166 °C (Kawashima et al. 1976)); ^{1}H NMR: δ = 7.15 (t, *J* = 7.8 Hz, 4H); 7.00 (d, *J* = 7.3 Hz, 4H); 6.95 (t, *J* = 7.3 Hz, 4H); 6.86 (d, *J* = 8.3 Hz, 4H); 6.53 (s, 4H); 3.85 (t, *J* = 6.3 Hz, 4H); 1.81 (quintet, *J* = 6.3 Hz, 2H); MS (EI): found *m/z* = 426; calcd. for $C_{31}H_{26}N_2$ 426; FTIR (nujol) ν = 1591; 1329; 1279; 1235; 1125; 903; 789; 758; 461 cm^{-1}.

*Compound **H***: 2-(5*H*-Dibenzo[*b,f*]azepin-5-yl)-acridine-9-carbaldehyde; m.p. 210–211 °C (acetone/water); ^{1}H NMR: δ = 11.17 (s, 1H), 8.75 (d, *J* = 8,8 Hz, 1H), 8.21 (d, *J* = 8,3 Hz, 1H), 8.0 (d, *J* = 9,2 Hz, 1H), 7.68–7.59 (m, 6H), 7.53 (d, *J* = 7,2 Hz, 2H), 7.45–7.46 (m, 3H), 7,12 (dd, J_1 = 9,2 Hz, J_2 = 1,6 Hz, 1H), 6.90 (s, 2H). MS (EI): found *m/z* = 398 [M$^+$]; calcd. for $C_{28}H_{18}N_2O$ 398. FTIR (film) ν = 1678, 1625, 1607,1593, 1486, 1336, 1309, 1241, 1151, 1306, 755 cm^{-1}. UV-Vis (acetonitrile): λ_1 = 211 nm ($\varepsilon_1 = 2.75 \times 10^4$), λ_2 = 250 nm ($\varepsilon_2 = 2.38 \times 10^4$), λ_3 = 282 nm ($\varepsilon_3 = 3.49 \times 10^4$), λ_4 = 388 nm ($\varepsilon_4 = 4.55 \times 10^3$), λ_5 = 500 nm ($\varepsilon_5 = 5.74 \times 10^3$). Fluorescence: λ_{ex} = 282 nm, λ_{em} = 610 nm.

*Compound **I***: 5*H*-Dibenzo[*b,f*]azepine-5-carbaldehyde m.p. 130–132 °C (lit. 135–136 °C (Querner et al. 2004))

^{1}H NMR: δ = 6.87 (d, *J* = 11.7 Hz, 1H), 6.93 (d, *J* = 11.7 Hz, 1H), 7.31 (d, *J* = 7.1 Hz, 1H), 7.34–7.50 (m, 7H), 8.34 (s, 1H). MS (EI): found *m/z* = 221 [M$^+$], calcd. for $C_{15}H_{11}NO$ 221.

FTIR (nujol) ν = 1697, 1569, 1492, 1337, 1300, 1152, 792, 768, 729 cm^{-1}.

*Compound **K***: 5-(3-Hydroxypropyl)-5*H*-dibenzo[*b,f*]azepine, m.p. 116–117 °C (dichloromethane/hexane) (lit. 117 °C (Ohta et al. 1981)); ^{1}H NMR: δ = 7.33 (t, *J* = 7.3 Hz, 2H), 7.14 (d, *J* = 7.8 Hz, 2H), 7.10 (d, *J* = 8.3 Hz, 2H,), 7.06 (t, *J* = 7.3 Hz, 2H,), 6.84 (s, 2H), 3.92 (t, *J* = 6.3 Hz, 2H), 3.70 (t, *J* = 5.9 Hz, 2H), 3.10 (s, 1H), 1.82 (m, 2H). MS (EI): found *m/z* = 251 [M$^+$], calcd. for $C_{17}H_{17}NO$ 251. FTIR (nujol) ν = 3405, 1308, 1231, 1207, 1120, 1035, 971, 806, 769, 722, 568, 450 cm^{-1}.

*Compound **N***: *N*-(3-Hydroxypropyl)-9(10*H*)-acridone; m.p. 205–208 °C (chloroform/hexane) (lit. 209–210 °C (Ohta et al. 1981)); ^{1}H NMR: δ = 8.62 (d, *J* = 8.3 Hz, 2H), 7.75 (t, *J* = 8.3 Hz, 2H), 7.68 (d, *J* = 8.7 Hz, 2H), 7.32 (t, *J* = 7.8 Hz, 2H), 4.60 (t, *J*∼6 Hz, 2H), 3.92 (t, *J* = 5.8 Hz, 2H), 3.10 (s, 1H), 1.81 (quintet, *J* = 5.9 Hz, 2H). MS (EI): found *m/z* = 253 [M$^+$], calcd. for $C_{16}H_{15}NO_2$ 253. FTIR (nujol) ν = 3394, 1608, 1260, 1078, 1040, 751 cm^{-1}.

3.4. HPLC analysis

The mobile phase consisted of an acetonitrile-buffer (55:45, v/v) mixture at a flow rate of 1 ml/min. Buffer composition: 5 ml triethylamine was dissolved in 1000 ml water and the mixture was adjusted to pH 11.2 with phosphoric acid. When pure acetonitrile was the mobile phase the flow rates were 1 ml/min or 0.7 ml/min. All samples for HPLC analysis were dissolved in acetonitrile-water (37:63, v/v) mixture using 1 mg substance per 1 ml solvent. The injection volume was fixed at 10 µl. All analyses were carried out at room temperature using UV detection at 256 nm.

3.5. X-ray structural analysis of compound H

Single crystals of compound **H** were grown by slow evaporation of a solution in dichloromethane (red prisms).

X-Ray measurements were carried out on KM4CCD kappa-geometry diffractometer equipped with a Sapphire-2 CCD detector. Enhanced X-ray MoKα radiation source with a graphite monochromator was used. Determination of the elemental cell and data collection were carried out at 120K. The preliminary calculations were made using CrysAlis software package (Oxford Diffraction, 2008). The structure was solved by direct method and refined by full-matrix least squares procedure based on *F2*. Empirical absorption correction using spherical harmonics was implemented in SCALE3 ABSPACK scaling algorithm. Non-hydrogen atoms were refined with anisotropic displacement parameters. Final calculations were carried out using the SHELX-97 program package (Sheldrick 2008). *Supplementary data*: cif file for compound **H** was deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 748029 (CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK; E-mail: deposit@ccdc.cam.ac.uk).

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