Synthesis of [1]Benzopyrano[3,4-*b*][1,4]oxazines as Potential Antidepressants

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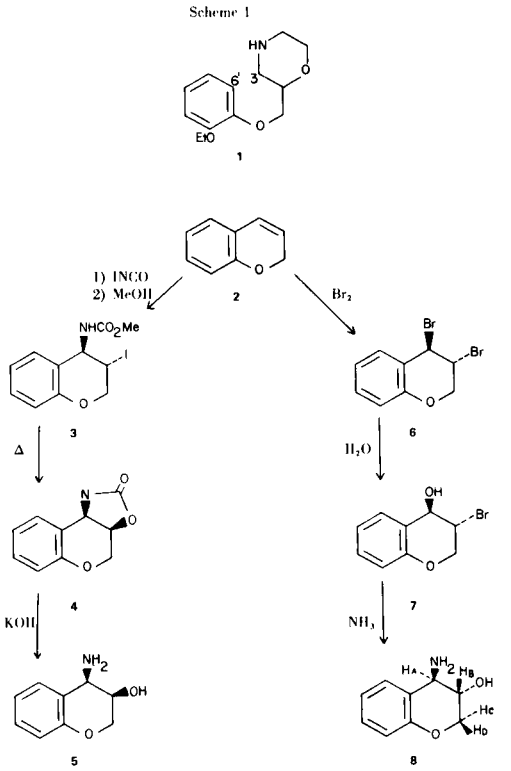
Stereospecific syntheses, from Δ-3-chromene, of *cis* and *trans*-4-aminochroman-3-ols, **5** and **8**, and their conversion into *cis* and *trans*-1,2,3,4a,5,10b-hexahydro[1]benzopyrano[3,4-*b*][1,4]-oxazines, **15** and **16**, are described.

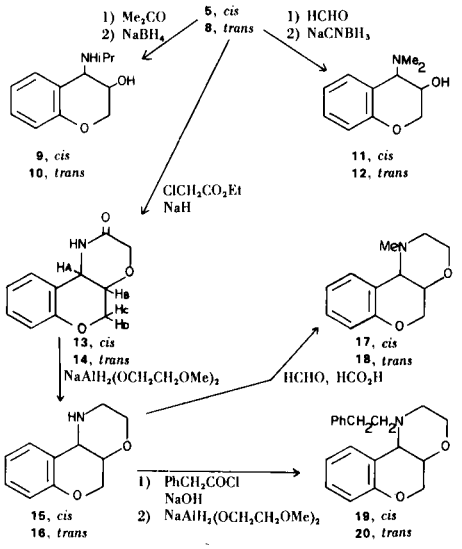
In an attempt to elucidate the preferred conformation for biological activity of the novel antidepressant viloxazine **1** (1), the *cis* and *trans*-1,2,3,4a,5,10b-hexahydro-[1]benzopyrano[3,4-*b*][1,4]oxazines, **15** and **16**, respectively, were synthesised. Such isomers represent restricted conformations of **1**, in which a carbon-carbon bond is formed between the 3 and 6′ positions.

Both **15** and **16** were synthesised independently by stereospecific routes. Key intermediates were the *cis* and *trans*-4-aminochroman-3-ols, **5** and **8**, respectively. Stereospecific syntheses of these isomers were achieved from the common intermediate Δ-3-chromene, **2** by the routes outlined in Scheme 1.

Scheme 1



Scheme 2

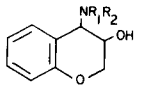


The construction of **5** from the *trans*-iodocarbamate **3** *via* the oxazolidinone **4** presupposes the *cis* stereochemistry (2). The *trans*-aminochromanol **8** would be the expected product from the bromohydrin **7** presumably *via* the corresponding epoxide (3). The pmr spectra of **5** and **8** were complicated by overlapping chemical shifts, although the *trans* stereochemistry of **8** was demonstrated by a 220 MHz spectrum (JAB = 6.3 Hz). However, the spectra of the corresponding oxazinones, **13** and **14**, clearly demonstrated the ring junction stereochemistry (see later). That **5** and **8** were different to the isomeric *cis* and *trans*-3-aminochroman-4-ols (4) was further demonstrated by their melting points.

These aminochromanols were further elaborated by standard methods to the corresponding isopropyl derivatives **9** and **10** and the dimethyl derivatives **11** and **12** (Scheme 2). All 4-aminochroman-3-ols synthesised are summarised in Table 1.

Table 1

4-Aminochroman-3-ols



Compound No.	Stereo-Chemistry	R_1	R_2	Yield %	Recrystallization Solvent (a)	M.p., °C	Formula	Analyses, % Calcd. C	H	N	Found C	H	N
5	*cis* (b)	H	H	94	A	112	$C_9H_{11}NO_2$	65.5	6.7	8.5	65.1	6.8	8.2
8	*trans* (b)	H	H	75	A	103-104	$C_9H_{11}NO_2$	65.5	6.7	8.5	65.2	6.6	8.6
9	*cis*	iPr	H	99	E	86-88	$C_{12}H_{17}NO_2$	69.6	8.2	6.8	70.0	8.2	6.6
10	*trans*	iPr	H	75	E	111	$C_{12}H_{17}NO_2$	69.6	8.2	6.8	69.3	8.1	6.6
11	*cis*	Me	Me	30	E/P	80	$C_{11}H_{15}NO_2$	68.4	7.8	7.3	68.1	7.6	6.9
12	*trans*	Me	Me	82	T	140-142	$C_{11}H_{15}NO_2(CO_2H)_2$	55.1	6.0	5.0	54.8	6.0	5.1

(a) A = ethyl acetate, E = ether, P = 60-80 petroleum ether, T = ethanol, M = methanol. (b) These isomers could also be distinguished by tlc (20% methanol-chloroform; Merck Kieselgel 60 0.25 mm, plates), **5**, Rf = 0.22; **8**, Rf = 0.31.

Conversion of both **5** and **8** into the oxazines **15** and **16** was carried out as described in Scheme 2. Further modifications of **15** and **16** to the *N*-methyl derivatives, **17** and **18**, and the *N*-phenylethyl derivatives, **19** and **20**, respectively were also performed (Scheme 2). All oxazines synthesised are summarised in Table 2.

The differing stereochemistries at the oxazine ring junction in the two series were most readily demonstrated by the 90 MHz proton spectra of the oxazinones **13** and **14**, using europium III shift reagents. Compound **13** exhibited a coupling constant of JAB = 4.0 Hz in keeping with the postulated *cis* stereochemistry. Compound **14** possessed a coupling constant of JAB = 9.1 Hz as required by the postulated *trans* structure (5).

Neither of the oxazines **15** and **16** exhibited anti-depressant activity in rodents at doses up to 30 mg./kg^{-1}.

EXPERIMENTAL

Melting points were determined on a Büchi melting point apparatus in open capillaries and are uncorrected. Infrared spectra were determined in chloroform solutions, or in nujol mulls where the compound was chloroform-insoluble. Pmr spectra were determined on a Varian HA100D instrument, with the exceptions of **13** and **14** which were analysed on a Bruker Spectrospin 90 MHz instrument, and **8** which was analysed on a Varian HR-200 instrument. Mass spectra were measured using a Hitachi-Perkin-Elmer RMU-6E instrument.

Elemental analyses were determined by the Physical Methods Section of I. C. I. Ltd. All compounds described exhibited satisfactory spectroscopic data.

Solvents were evaporated under reduced pressure. Recrystallisation solvents, yields, and melting points are recorded in the tables.

2-Oxo-1,3a,4,9b-tetrahydro-2*H*[1]benzopyrano[4,3-*d*]oxazole (**4**).

Silver cyanate (69 g.) and iodine (65 g.) were stirred for ½ hour in ether (150 ml.). The reaction mixture was then cooled (ice-water bath) and a solution of Δ-3-chromene (6) (50.2 g.) in ether (300 ml.) was added dropwise. The suspension was stirred vigorously at room temperature for a further 4 hours and the excess silver salts filtered off. Methanol (400 ml.), and a few drops of a solution of lithium methoxide in methanol, were added to the filtrate which was then left at room temperature overnight. Solvents were then evaporated, and the residue redissolved in a small volume of ether, washed with water, dried, and evaporated to yield **3** which was recrystallised from ether (72%). Iodocarbamate **3** (10 g.) in diethylene glycol (150 ml.) was refluxed for 24 hours. After evaporation of solvent, the dark-brown residue was recrystallised from ethyl acetate to yield **4**, m.p. 184° (76%).

cis-4-Aminochroman-3-ol (**5**).

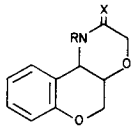
Methanolic potassium hydroxide (0.85 *N*) (250 ml.) was added to a suspension of **4** (4.4 g.) in water (50 ml.) and the mixture refluxed for 16 hours. Methanol was evaporated, and the aqueous residue extracted with chloroform which was dried and evaporated. The light-brown residue was recrystallised to yield fine white needles; mass spectrum: m/e 165 (12%), 149 (4), 121 (100), 93 (30), 44 (21); pmr (deuteriochloroform): δ 2.3 (broad, 3H, -NH_2, -OH), 4.0 (broad, 4H, -CH-N, -CH-O-, CH_2-O), 6.8-7.4 (m, 4H, aromatics). Attempts at further resolution of the 4.0 δ peak using 90 and 220 MHz instruments and a variety of solvents did not yield satisfactory data to enable the *cis* stereochemistry to be unequivocally established at this stage in the synthesis.

trans-4-Aminochroman-3-ol (**8**).

A solution of bromohydrin **7** (7), (45.5 g.) in methanol (500 ml.) was added over 1 hour to an ice-cooled solution of 0.880 ammonia (800 ml.) in methanol (400 ml.). The solution was stirred at room temperature overnight, solvent evaporated, and the residue partitioned between chloroform and dilute aqueous sodium hydroxide. The chloroform extract was washed, dried, and evaporated, and the residue recrystallised; mass spectrum: m/e 165 (8%), 149 (6), 121 (100), 93 (20), 43 (24); pmr (deuteriochloroform:DMSO-d_6; 10:1): δ 2.8 (broad, 3H, -NH_2, -OH), 3.5-4.2 (m, 4H, -CH-N, -CH-O, -CH_2-O), 6.7-7.4 (m, 4H, aromatics). Further analysis at 220 MHz exhibited coupling constants of JAB = 6.3 Hz (indicative of axial-axial coupling and therefore *trans* substituents), JBC = 6.3, JBD = 2.8, JCD = 11.7.

Table 2

[1]Benzopyrano[3,4-*b*][1,4]oxazines



Compound No.	Stereo-Chemistry	R	X	Yield, %	Recrystallization Solvent (a)	M.p., °C	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
13	*cis* (b)	H	O	62	A	200	$C_{11}H_{11}NO_3$	64.4	5.4	6.8	64.3	5.4	6.6
14	*trans* (b)	H	O	50	A	227-230	$C_{11}H_{11}NO_3$	64.4	5.4	6.8	64.3	5.5	7.3
15	*cis*	H	H_2	45	T	159	$C_{11}H_{13}NO_2$ $(CO_2H)_2$	55.5	5.3	4.9	55.1	5.1	5.0
16	*trans*	H	H_2	52	M	205	$C_{11}H_{13}NO_2$ $½(CO_2H)_2 \cdot CH_3OH$	58.2	6.7	5.2	58.6	6.5	5.0
17	*cis*	Me	H_2	48	M	204	$C_{12}H_{15}NO_2$ $(CO_2H)_2$	56.9	5.8	4.7	57.0	5.7	5.0
18	*trans*	Me	H_2	27	T	162	$C_{12}H_{15}NO_2$ Monomaleate	60.0	5.9	4.4	60.4	5.7	4.2
19	*cis*	$PhCH_2CH_2$	H_2	30	T	171	$C_{19}H_{21}NO_2$ $(CO_2H)_2 \cdot H_2O$	62.5	6.2	3.6	62.7	5.9	3.8
20	*trans*	$PhCH_2CH2$	H_2	20	T	204 dec.	$C_{19}H_{21}NO_2$ HCl	68.7	6.6	4.2	68.4	6.5	4.0

(a) See Table 1. (b) These isomers could also be distinguished by tlc (20% methanol-chloroform; Merck Kieselgel 60 0.25 mm plates), **13**, Rf = 0.54; **14**, Rf = 0.67.

trans-4-Isopropylaminochroman-3-ol (**10**).

A mixture of aminochromanol **8** (5.0 g.), sodium acetate trihydrate (8.1 g.), acetic acid (25.2 ml.), acetone (15 ml.) and water (25 ml.) was cooled to 0° with stirring. Sodium borohydride (6.0 g.) was added portionwise over a period of 15 minutes. After neutralisation with concentrated sodium hydroxide solution, the mixture was repeatedly extracted with ether. The combined ether washings were dried, evaporated and the residue recrystallised. The *cis* isomer **9** was prepared in a like manner from **5**.

cis-4-Dimethylaminochroman-3-ol (**11**).

Sodium cyanoborohydride (1 g.) was added to a stirred solution of aminochromanol **5** (1.65 g.) and 37% formaldehyde (4 ml.) in acetonitrile (15 ml.). After 15 minutes the solution was neutralised to *p*H 6 with glacial acetic acid. After a further 45 minutes stirring, solvents were evaporated, and 2*N* aqueous potassium hydroxide (20 ml.) added. The mixture was extracted with ether (100 ml.) and the ether layer washed, dried and evaporated. The pale-yellow residue was twice recrystallised. Compound **12** was similarly prepared from **8**.

cis-1,4a,5,10b-Tetrahydro-3*H*[1]benzopyrano[3,4-*b*][1,4]oxazin-2-one (**13**).

Sodium hydride 60% (3.4 g.) was added with stirring to a solution of aminochromanol **5** (10.0 g.) in sodium-dried benzene (250 ml.). The resulting solution was cooled, ethyl chloroacetate (8.2 g.) added, and the mixture stirred under nitrogen for 3 hours. Solvent was evaporated under reduced pressure, the residue dissolved in chloroform and washed with water, 2*N* hydrochloric acid and water. The chloroform was dried, evaporated under reduced pressure, and the residue recrystallised. Compound **14** was similarly synthesised from **8**.

Both **13** and **14** exhibited indistinct 100 MHz pmr spectra, (deuteriochloroform: DMSO-d_6; 10:1); **13**: δ 4.0-4.6 (m, 6H, H_A, H_B, H_C, H_D, - CH_2-CO), 6.6-7.5 (m, 4H, aromatics), 9.0 (d, 1H, -NH); **14**: 3.8-4.6 (m, 6H, H_A, H_B, H_C, H_D, - CH_2CO), 6.7-7.6 (m, 4H, aromatics), 8.9 (broad, 1H, -NH). The ring junction stereochemistry in both isomers was finally determined from 90 MHz spectra in deuteriochloroform using tris(1,1,1,2,-2,3,3,)heptafluoro-7,7-dimethyl-4,6-octanedione europium III; **13**: JAB = 4.0, JBC = 0, JBD = 2.6, and JCD = 12.3 Hz; **14**: JAB = 9.1, JBC = 4.7, JBD = 10.2, and JCD = 10.4 Hz.

cis-1,2,3,4a,5,10b-Hexahydro[1]benzopyrano[3,4-*b*][1,4]oxazine (**15**).

A 70% solution of sodium dihydrobis(2-methoxyethoxy)-aluminate in benzene (17.5 g.) was slowly added to a solution of oxazinone **13** (5.0 g.) in dry THF (200 ml.). The mixture was refluxed with stirring under nitrogen for 3 hours. Solvents were then evaporated and the residue partitioned between ether and dilute aqueous sodium hydroxide. The ether layer was extracted with dilute hydrochloric acid, which was then neutralised and extracted with ether. The organic layer was dried, evaporated, and residue dissolved in acetone and excess oxalic acid added. The white oxalate salt which precipitated was then recrystallised. Compound **16** was similarly synthesised from **14**.

1-Methyl-1,2,3,4a,5,10b-hexahydro[1]benzopyrano[3,4-*b*][1,4]-oxazine (**17**).

Oxazine **15** (1.0 g.) was added to a mixture of 90% formic acid solution (1 ml.) and 37% formaldehyde solution (0.6 ml.), and the mixture heated at 100° for 5 hours. The reaction mixture was cooled and concentrated hydrochloric acid (0.86 ml.) added. The solution was neutralised with aqueous sodium hydroxide, extracted with benzene, and the organic solvent dried and evaporated. The residue was dissolved in a small volume of acetone and an excess of an acetone solution of oxalic acid added. The oxalate salt was collected and recrystallised. Compound **18** was prepared from **16** in a similar fashion.

cis-1-Phenethyl-1,2,3,4a,5,10b-hexahydro[1]benzopyrano[3,4-*b*]-[1,4]oxazine (**19**).

A solution of sodium hydroxide (0.24 g.) in water (1 ml.) was added to a solutionof oxazine **15** (1.0 g.) in ether (15 ml.). A solution of α-phenylacetyl chloride (0.7 ml.) in ether (1 ml.) was added dropwise, and the suspension stirred vigorously for 1 hour. The mixture was extracted with benzene, and the organic extract washed with dilute hydrochloric acid, water, dried and evaporated. The resultant colourless gum (1.8 g.) was dissolved in dry THF (100 ml.), a 70% solution of sodiumdihydrobis(2-methoxyethoxy) aluminate in benzene (4.0 g.) added dropwise and the reaction mixture refluxed for 2 hours. The work-up procedure was the same as for compound **15** and the oxalate salt was prepared in the same way. A similar method was used to prepare **20** from **16**.

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