A New, Convenient Synthesis of Glafenine and Floctafenine

Gilbert MOUZIN, Henri COUSSE, Jean Marie AUTIN

Centre de Recherche Pierre Fabre, 17 Avenue Jean Moulin, F-81106 Castres, France

Glafenine [α-glyceryl *N*-(7-chloro-4-quinolyl)-anthranilate; **5**] and Floctafenine [α-glyceryl *N*-(8-trifluoromethyl-4-quinolyl)-anthranilate; **6**] are the common, international, proprietry names of two analgesically active substances* with no anti-inflammatory action.

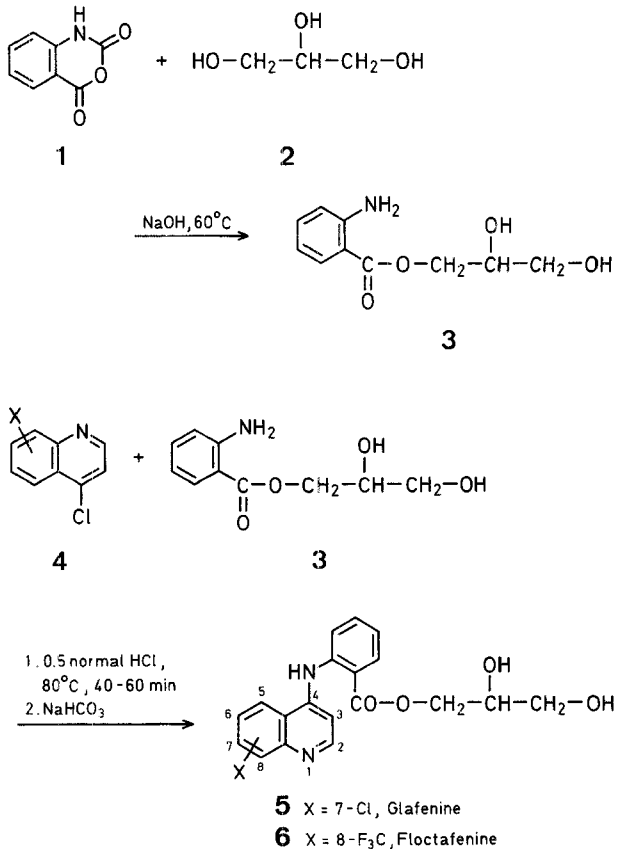
At present these compounds are prepared by the Allais method[1-5] [(a) and (b)] and by the milder Pavao method[6] (c).

(a) 4-Chloroquinoline undergoes condensation with methyl anthranilate, the resultant methyl ester is transesterified with glyceryl acetonide, and the acetonide moiety is hydrolysed.

(b) Glyceryl acetonide is esterified by *o*-nitrobenzoyl chloride, the nitro group is reduced to an amino group, the resultant glyceryl acetonide anthranilate is condensed with 4-chloroquinoline, and the acetonide moiety is hydrolysed.

(c) Glyceryl *o*-chlorobenzoate undergoes condensation with a 4-aminoquinoline.

Methods (a) and (b) are relatively long (4 stages) and Method (c) is not very competitive as the intermediates are expensive and/or difficult to prepare; also the aminoquinoline has only low reactivity. Thus, we have developed a more competitive synthesis, which may also be useful for industrial purposes, based on the new intermediate α-glyceryl anthranilate[7] **(3)**.



5 X = 7-Cl, Glafenine

6 X = 8-F_3C, Floctafenine

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Intermediate **3** is obtained in quantitative yield by reaction of the commercially available[8] and readily available[9] isatoic anhydride (**1**) with excess glycerol (**2**) in the presence of sodium hydroxide. The glycerol solution of **3** is then treated with 4,7-dichloroquinoline (**4**, X = 7-Cl) to give **5**[10] or with 4-chloro-8-trifluoromethylquinoline (**4**, X = 8-F_3C) to give **6**[11].

α-Glyceryl Anthranilate (3):
Glycerol (**2**; 2.93 kg, 31.8 mol) and sodium hydroxide pellets (15.7 g, 0.39 mol) are charged into a 10 litre reactor. Isatoic anhydride (**1**; 510 g, 3.1 mol) is then added and the reaction mixture is slowly warmed to 60 °C. The evolved carbon dioxide is trapped by extractor and the mixture is heated at 80 °C for 1 h. At this stage the yield is quantitative and this glycerol solution can be used for the preparation of **5** and **6**.

An analytical sample was obtained by evaporation of the glycerol under reduced pressure and chromatography of the residue on a column of silca gel with ethanol as eluent; m.p. 90 °C (recrystallised from 1:1 chloroform/ethanol).

$C_{10}H_{13}NO_4$	calc.	C 56.86	H 6.20	N 6.63
(211.2)	found	56.51	6.21	6.71

I.R. (KBr): ν = 3500–3400 (NH_2); 3300 (OH); 1690 cm^{-1} (C=O).

^{1}H-N.M.R. (CD_3OH): δ = 8.0–6.5 (m, $4H_{arom}$); 4.8 (s, 4H); 4.4 (d, 2H); 4.0 (m, 1H); 3.7 ppm (d, 2H).

α-Glyceryl *N*-(7-Chloro-4-quinolyl)-anthranilate (5; Glafenine):
To a glycerol solution of **3** (~2.8 l, corresponding to 654.7 g, 3.12 mol of **3**), obtained as described above, is added 0.5 normal hydrochloric acid (6.63 l) and 4,7-dichloroquinoline (**4**; X = 7-Cl; 520 g, 2.63 mol). The reaction mixture is heated at 80 °C for 40 min, cooled to 20 °C, and transferred to a 20 litre vessel. The mixture is treated with 0.9 normal sodium hydroxide solution (6 l) and neutralisation is completed by addition of solid sodium hydrogen carbonate (~50 g). Glafenine slowly crystallises out and is purified by recrystallisation from chloroform or by conversion to the hydrochloride and subsequent regeneration of the free base. The product is then dried in a vacuum oven (80 °C/15 torr) for 24 h; yield: 65–75%; m.p. 169–170 °C; Lit. [2] m.p. 170 °C.

I.R. (KBr): ν = 3500, 3100 (OH+NH); 1680 (C=O); 1620–1580 cm^{-1} (C=C_{arom}).

^{1}H-N.M.R. (DMSO-d_6): δ = 8.7–7.0 (m, $9H_{arom}$); 4.4 (d, 4H); 3.8 (m, 1H); 3.5 ppm (d, 2H).

α-Glyceryl *N*-(8-Trifluoromethyl-4-quinolyl)-anthranilate (6; Floctafenine):
To a glycerol solution of **3** (~2.8 l, corresponding to 654.7 g, 3.12 mol of **3**) obtained as described above, is added 1 normal hydrochloric acid (3.3 l) and 4-chloro-8-trifluoromethylquinoline (**4**; X = 8-F_3C; 530 g, 2.29 mol). The mixture is heated at 80 °C for 1 h, allowed to cool to room temperature, and neutralised by addition of 1 normal sodium hydrogen carbonate solution (~4.5 l). The coarse Floctafenine crystallises out and is purified either by recrystallisation from 1:1 chloroform/ethanol or by conversion to the hydrochloride and regeneration of the free base; yield: 60–80%; m.p. 179–180 °C; Lit. [4] m.p. 180 °C. The I.R. and ^{1}H-N.M.R. spectra are identical to those of an authentic sample prepared by Method (a).

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* Trade names of commercial products: Glifanan, Glifan, Adalgur, Idarac marketed by Laboratoires Hoechst-Roussel.

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6 M. Pavao, M. Mladen, *German Patent* 2251646, C. R. C. (1972); *C. A.* **81**, 25 400 (1974).

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