***SHORT PAPER***

*J. Chem. Research (S)*, 2003, 36-37

# A novel synthesis of 2- diethylamino-3-*o*-nitrobenzylquinolines†

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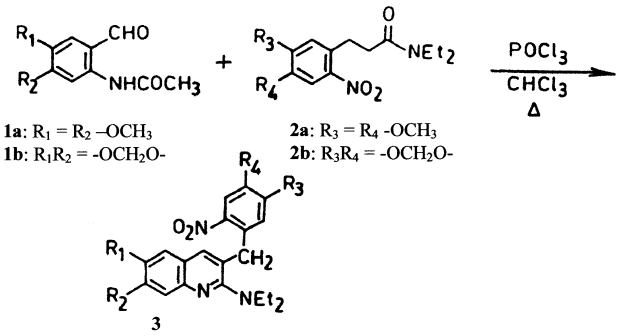
Four hitherto unknown 2-diethylamino-3-*o*-nitrobenzylquinolines have been prepared by the reaction of a preformed 1:1 complex of β-aryl-*N,N*-diethylpropanamides and phosphorus oxychloride with o-acetamidobenzaldehydes.

**Keywords:** quinolines, *t*-amides, *o*-acetamidobenzaldehyde

The synthesis of 2-amino-3-*o*-nitrobenzylquinolines has been carried out with a view to the *in vivo* activities associated with 2-(2-dimethylaminoethyl)thienyl-3-benzylquinoline, which is reported to have 5-hydroxytryptamine antagonist activity and antagonism of hyperthermia induced by fenfluramine in the rat.[1]

The reported methods for the synthesis of 3-benzylquinolines involve reduction of 3-benzoylquinolines, either photochemically[2] or by the Huang Minlon method.[3] β-Arylamino-α-benzylacroleins also afford 3-benzylquinolines on heating with aluminium chloride.[4] 2-Substituted 3-benzylquinolines can be obtained by displacement of a 2–chloro qroup with a suitable nucleophile.[1] The methodology adopted by us for the synthesis of 3-*o*-nitrobenzylquinolines (**3a–d**) is shown in Scheme 1. This involves the reaction between *o*-acetamidobenzaldehydes **la**,**b**[5] and preformed complexes of the hitherto unknown *N,N*-diethylpropanamides **2a**,**b** and phosphorus oxychloride. The substituted propanamides (**2a**,**b**) were prepared from the corresponding dihydrocinnamoyl chlorides and diethylamine. When a reaction between *o*-acetamidobenzaldehyde **1a** and amide **2a** was performed, a gummy solid was obtained, which was purified by column chromatography to afford a solid, m.p. 107 °C. The $^1$H NMR data (see Experimental) coupled with the mode of formation and elemental analysis showed this compound to be the desired 3-benzylquinoline **3a**. In a similar way 3-*o*-nitrobenzyl quinolines **3b–d** were prepared in yields of 60-70%. This clearly demonstrated the utility of the present method for the synthesis of 2-diethylamino-3-*o*-nitrobenzylquinolines.




**3a** $R_1 = R_2 = R_3 = R_4 = -OCH_3$
**3b** $R_1 = R_2 = -OCH_3, R_3R_4 = -OCH_2O-$
**3c** $R_1R_2 = R_3R_4 = -OCH_2O-$
**3d** $R_1R_2 = -OCH_2O-, R_3 = R_4 = -OCH_3$

**Scheme 1**

## Experimental

*Preparation of β aryl-N,N-diethylpropanamides* (**2a,b**)**:** A mixture of the nitro-acid (3g) and thionyl chloride (12ml) was refluxed on an oil bath for 3.5 hours. Excess of thionyl chloride was removed under vacuum. The resulting acid chloride was added dropwise to an ice-cold solution of diethylamine (10ml) in chloroform (10ml). After addition was complete the stirring was continued for 1.5 hours. The product was neutralised by addition of dilute HCl and extracted with chloroform (15ml). The chloroform layer was washed, dried (anhydrous $Na_2SO_4$) and evaporated to furnish a gummy product. Purification by column chromatography (silica) using petroleum ether-ethyl acetate (7:3) mixture (eluant), afforded the yellow crystalline nitro-amides.

*Dimethoxy compound* **2a**: yield 80%, m.p. 98 °C; IR: 1640 cm$^{-1}$, $^1$HNMR (δ): 7.80 (1H, s, ArH *ortho* to $NO_2$), 7.05 (1H, s, ArH), 4.05 (3H, s, $OCH_3$), 4.00 (3H, s, $OCH_3$), 3.35 (6H, m, $3CH_2$), 2.70 (2H, t, *J* = 7 Hz, $CH_2$), 1.15 (6H,t, *J* = 7 Hz, $2CH_2CH_3$). Found: C, 57.98; H, 6.98. $C_{15}H_{22}N_2O_5$ requires: C, 58.06; H, 7.09%.

*Methylenedioxy compound* **2b**: yield 82%, m.p. 87 °C, IR: 1640 cm$^{-1}$, $^1$H NMR (δ): 7.45 (1H, s, ArH, *ortho* to $NO_2$), 6.95 (1H, s, ArH), 6.00 (2H, s, $OCH_2O$), 3.30 (4H, q, *J* = 7 Hz, 2 $NCH_2CH_3$) 3.10 (2H, t, *J* = 7 Hz, $CH_2Ar$), 2.60 (2H, t, *J* = 7 Hz, $CH_2CO$), 1.15 ( 6H, t, *J* = 7 Hz, 2 $NCH_2CH_3$). Found: C, 56.91; H, 5.98. $C_{14}H_{18}N_2O_5$ requires C, 57.13; H, 6.17 %.

*2-Diethylamino–3-o-nitrobenzyl-6,7-dioxyquinolines* **(3a–d):** Phosphorus oxychloride (1 mM) was added to a solution of the amide (**2a,b**) (1 mM) in dry chloroform (5ml), and the mixture was stirred at room temperature for 13 hours. To this was added the *o*-acetamidobenzaldehyde (**1a,b**) (1 mM) and the mixture was refluxed until the latter was consumed (TLC, 8 h). The cooled mixture was poured into aqueous sodium carbonate (10%, 10 ml), warmed on a water bath for 30 minutes, and cooled. The product was extracted with chloroform (2 X 10ml). The chloroform extract was washed, dried ($Na_2SO_4$) and evaporated. The gummy solid obtained was passed through a short column of silica and eluted with pet ether – ethyl acetate (9 : 1) mixture to afford compound **3a–d**.

**3a** ($R_1 = R_2 = R_3 = R_4 = OCH_3$): yield: 70%, m.p. 107 °C, IR: 1625cm$^{-1}$, $^1$HNMR: δ 7.70 (1H, s, C-4H), 7.40 (1H, s,C-3′-H) 7.33, 6.85 (each 1H, s, C-5 and C-8H), 6.70 (1H, s, C-6′H), 4.40 (2H, s, $CH_2$), 4.05, 4.00, 3.90, 3.80 (each 3H, s, $OCH_3$), 3.30 (4H, q, *J* = 7 Hz, $2NCH_2CH_3$), 1.20 (6H, t, *J* = 7 Hz, $2NCH_2CH_3$). Found: C, 63.33; H, 6.45; N, 9.25. $C_{24}H_{29}N_3O_6$ requires: C, 63.28; H, 6.42;N 9.24 %.

**3b** ($R_1 = R_2 = OCH_3$, $R_3R_4 = OCH_2O$): yield 60%, m.p. 136 °C, IR: 1625 cm$^{-1}$, $^1$H NMR: δ 7.55 (1H, s, C-4H), 7.40 (1H, s, C-3′H) 7.25, 6.86 (each 1H, s, C-5 and C-8H), 6.60 (1H, s, C-6′H), 6.05 (2H, s, $OCH_2O$) 4.30 (2H, s, $CH_2$) 4.00, 3.90 (each 3H, s, $OCH_3$), 3.30 (4H, q, *J* = 7 Hz, $2NCH_2CH_3$), 1.10 (6H, t, *J* =7Hz, 2 $NCH_2CH_3$), 1.10 (6H, t, *J* = 7Hz, $2NCH_2CH_3$). Found: C, 62.83; H, 5.79; N, 9.55. $C_{23}H_{25}N_3O_6$ requires C, 62.86; H, 5.73; N, 9.57 %.

**3c** ($R_1R_2 = R_3R_4 = OCH_2O$): yield 62%, m.p. 147 °C, IR: 1625 cm$^{-1}$, $^1$H NMR: δ 7.55 (1H, s, C-4H), 7.35 (1H, s, C-3′H), 7.25, 6.80 (each 1H, s, C-5 and C-8 H), 6.55 (1H, s, C-6′H), 6.05, 6.00 (each 2H, s,$OCH_2O$), 4.30 (2H, s, $CH_2$), 3.30 (4H, q, *J* = 7 Hz, 2 $NCH_2CH_3$) 1.10 (6H, t, *J* = 7 Hz, 2 $NCH_2CH_3$). Found: C, 62.42, H, 4.97; N, 9.91. $C_{22}H_{21}N_3O_6$ requires C, 62.40; H, 5.00; N, 9.93 %.

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

**3d** ($R_1R_2$ = $OCH_2O$, $R_3$ = $R_4$ = $OCH_3$): yield 65 %, m.p. 131 ºC, IR: 1625 $cm^{-1}$, $^1H$ NMR: δ: 7.70 (1H, s, C-4H), 7.30 (1H,s, C-3′H), 7.20, 6.80 (each 1H,s, C-5 and C-8H), 6.60 (1H, s, C-6′ H), 6.00 (2H,s, $OCH_2O$), 4.28 (2H,s, $CH_2$), 3.95, 3.80 (each 3H, s, $OCH_3$) 3.30 (4H q, *J* = 7Hz, $2NCH_2CH_3$), 1.10 (6H, t, *J* = 7 Hz, 2 $NCH_2CH_3$), Found: C, 62.88; H, 5.70; N, 9.58. $C_{23}H_{25}N_3O_6$ requires C, 62.86; H, 5.73; N, 9.57 %.

*Received 4 May 2002; accepted 10 August 2002*
*Paper 02/1368*

## References

1 D.N. Middlemiss R.J. Pearce, and C.W. Thornber, *J. Med. Chem.*1987, **30**, 2252.
2 A.C. Plasz, E.V. Brown, and H.H. Bauer, *J. Chem. Soc. Chem. Comm.*, 1972, 527.
3 E.V. Brown, A. C. Plasz, R. Isbrandt, and H.H. Bauer, *Org. Prep. Proc. Int*, 1974, **6**, 239.
4 R. Todoriki, M. Ono, and S. Ramura, *Chem. Pharm. Bull.*, 1983, **31**, 4277.
5 A.Rilliet and L.Krietman, *Compt. Rend.* **157**, 782 (*Chem. Abstr*. 1914, **8**, 659); W.Borsche and W. Reid, *Ber.* 1943, **76**, 1011.