Reactions of 5-phenyl-1,2,4-triazin-3-one with indoles and *ortho*-phenylenediamine

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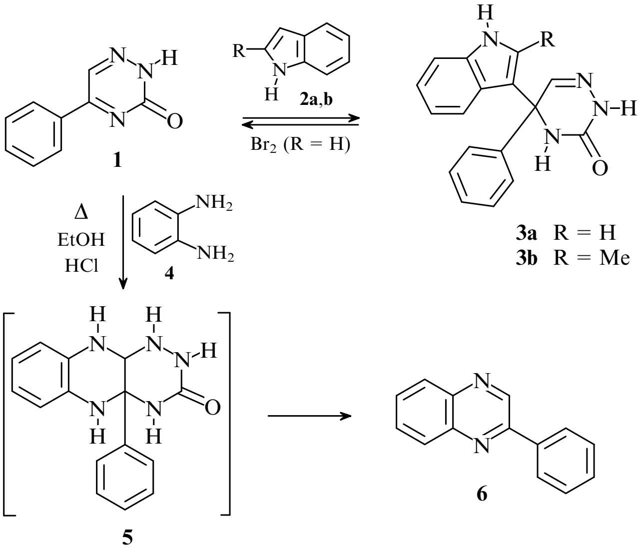
5-(Indol-3-yl)-5-phenyl-3-oxo-2,3,4,5-tetrahydro-1,2,4-triazines 3a,b have been obtained upon treatment of 5-phenyl-1,2,4-triazin-3(2*H*)-one 1 with indoles 2a,b; the starting material 1 was regenerated when 3a was treated with bromine in acetic acid, and the reaction of 1 with *ortho*-phenylenediamine 4 in the presence of HCl yielded 2-phenylquinoxaline 6.

The ability of 1,2,4-triazin-3-ones to add O- and C-nucleophiles to give a C-5 adduct is well known.[1] Only a few examples of the addition of cyclic amines to the 5-position of 1,2,4-triazin-3-ones have been reported.[2] There is one report in the literature that nucleophilic attack at the 5-position of 1,2,4-triazin-3-ones is blocked by bulky substituents.[3]

We did not observe any steric hindrance due to a 5-phenyl group in the addition of indoles to the 5-position. Thus, 5-phenyl-1,2,4-triazin-3(2*H*)-one **1** reacted with the indoles **2a**,**b** in boiling ethanol with a catalytic amount of HCl to give 5-(indol-3-yl)-5-phenyl-3-oxo-2,3,4,5-tetrahydro-1,2,4-triazines **3a**,**b** (Scheme 1).[†]



Scheme 1

For the complete transformation of **1** into **3a** the reaction mixture needed 5 min in boiling ethanol. However, for the synthesis of **3b** from **1** and 2-methylindole **2b**, 3 h in refluxing ethanol–HCl were required.

The structures **3a**,**b** were confirmed by their ^{1}H, ^{13}C NMR and mass spectroscopy data.[‡] In both mass spectra the observed base peak is [M$^+$ – Ph], together with intensive M$^+$ and [M$^+$ – Ph – 70]$^+$ peaks. The loss of 70 mass units from the [M – Ph]$^+$ ion is due to the loss of a [HC=NNHCO] fragment, and this is only possible if the indole substituent is not bound to C-6 of the 1,2,4-triazine ring.

The sp^3 signal for C-5 without a $^1J_{\mathrm{CH}}$ coupling constant at 58.96 ppm in the ^{13}C NMR spectrum of **3a** unequivocally confirms that the addition of the indole took place at this position (Figure 1). The chemical shifts for C-3 and C-6 in the ^{13}C NMR spectrum of **3a** are in agreement with the proposed structure. The signal for C-6 is, compared to **1**, shifted downfield by 9.52 ppm and the signal for C-3 upfield by 2.79 ppm (Figure 2).

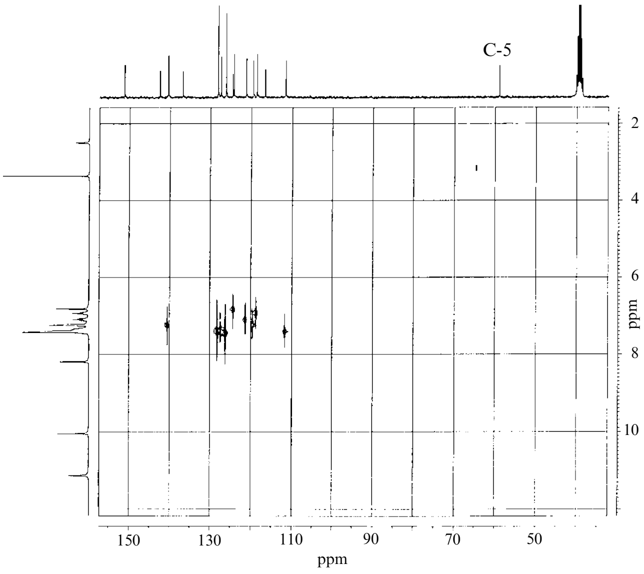


Figure 1 CH correlation for **3a**.

Both **3a** and **3b** are colourlees and thermally stable with high melting points. An unexpected regeneration of **1** from **3a** was observed upon addition of bromine in acetic acid.[§] This can be explained by the addition of bromine to the indole

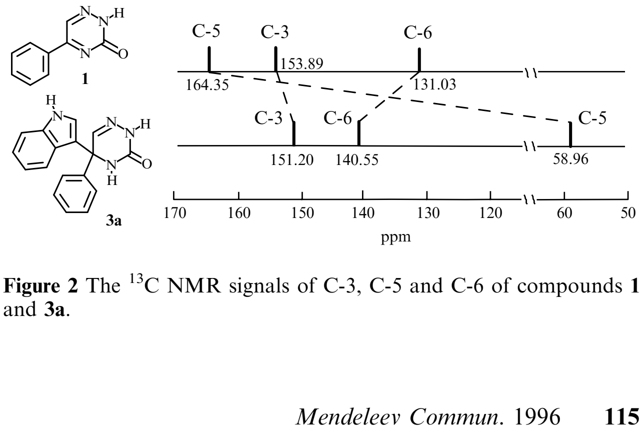


Figure 2 The ^{13}C NMR signals of C-3, C-5 and C-6 of compounds **1** and **3a**.

[†] *Synthesis of 5-(indol-3-yl)-5-phenyl-3-oxo-2,3,4,5-tetrahydro-1,2,4-triazine* **3a**: a mixture 5-phenyl-1,2,4-triazin-3(2*H*)-one **1** (1.0 mmol) and indole **2a** (1.1 mmol) was refluxed in ethanol (5 ml) and HCl (10%, 0.5 ml) for 5 min. The crystalline product was filtered off and reprecipitated from DMF with water to give **3a** (101 mg, 70%) with mp > 250 °C; *m*/*z* 290 (M$^+$).

Synthesis of 5-(2-methylindol-3-yl)-5-phenyl-3-oxo-2,3,4,5-tetrahydro-1,2,4-triazine **3b**: a mixture of **1** (1.0 mmol) and 2-methylindole **2a** (1.1 mmol) was refluxed in ethanol (5 ml) and HCl (10%, 0.5 ml) for 3 h. The mixture was evaporated to dryness under vacuum. The residue was washed with ethanol (2 ml) and reprecipitated from DMF with water to give **3b** (47 mg, 26%) with mp > 250 °C; *m*/*z* 304 (M$^+$).

[‡] *Spectral data for* **3a**. ^{1}H NMR (300 MHz; [^{2}H$_6$]DMSO): 6.70–7.50 (11H, m, CH$_{\mathrm{arom}}$, CH$_{\mathrm{indol}}$, C$_6$H$_{\mathrm{triazin}}$), 8.19 (1H, s, NH), 10.04 (1H, s, NH), 11.13 (1H, s, NH); ^{13}C NMR (75 MHz): 58.96, 111.76, 116.75, 118.72, 119.61, 121.31, 124.29, 124.61, 126.20, 127.45, 128.19, 136.91, 140.55, 142.61, 151.20.

substituent and the resultant formation of intermediate **7**. Subsequent elimination of HBr and 3-bromoindole affords **1**. This transformation can also proceed *via* the intermediate **8** (Scheme 2).

2-Phenylquinoxaline **6** was isolated upon heating **1** with *ortho*-phenylenediamine **4** in ethanol with catalytic amounts of HCl.[¶] A similar reaction has been observed when 1-alkyl-1,2,4-triazinium salts were reacted with **4**.[2,4] Therefore the intermediate formation of the cyclic addition product **5** in the reaction of **1** with **4** seems to be highly likely.

This work was supported by the Volkswagen-Foundation.

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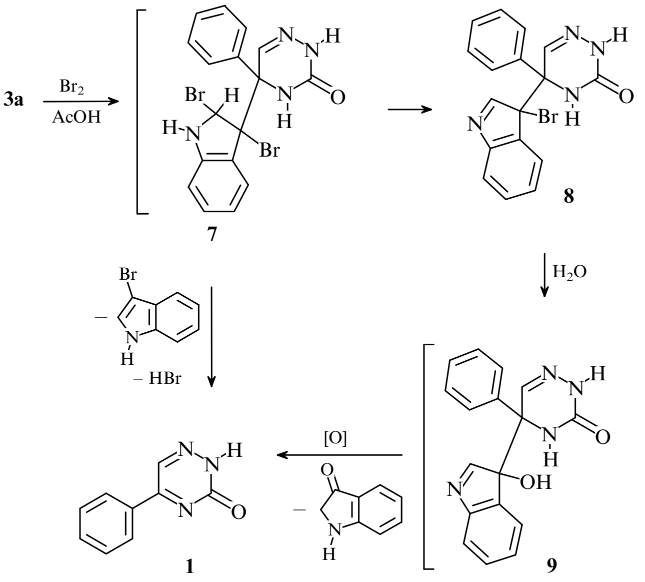

Scheme 2

Received: Moscow, 20th November 1995
Cambridge, 9th January 1996; Com. 5/07780J

[§] A solution of **3a** (0.2 mmol) and Br_2 in acetic acid (3 ml) was stirred for 20 min. The precipitate was filtered off and recrystallized from water to give **1** (21 mg, 61%).

[¶] *Synthesis of 2-phenylquinoxaline* **6**: 5-Phenyl-1,2,4-triazin-3(2*H*)-one **1** (0.5 mmol) and *ortho*-phenylenediamine **4** (0.5 mmol) were refluxed in ethanol (3 ml) and HCl (35%, 0.04 ml) for 5 h. The resulting solution was evaporated to dryness under vacuum, and the residue reprecipitated from DMF with water to give **6** (35 mg, 34%) with mp 77 °C (lit.,[5] 78 °C).