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New Synthesis of Pyrrolo[1,2-*a*]indole Derivatives

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A new synthesis of 2*H*-pyrrolo[1,2-*a*]indole-3,9-dione derivatives **5a,b** is reported, based on the reaction of 1-acetyl-2-dialkylaminomethyleneindolin-3-ones with formamide acetals.

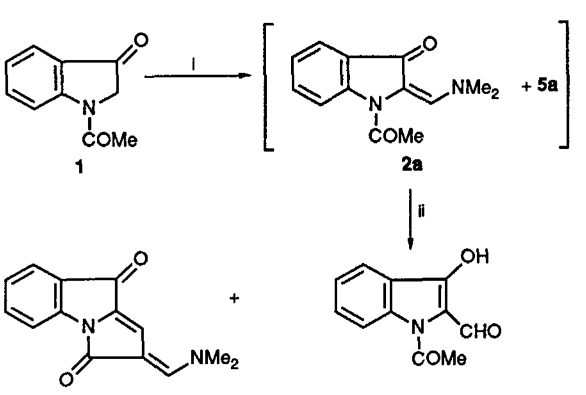
It is known that amide acetals react smoothly with active methylene compounds to yield the corresponding enamines.[1,2] Recently, we have used *N*-acetylindolin-3-one **1** as an active methylene component to form 2-dialkylaminomethyleneindolin-3-ones **2**, which are suitable starting substances for the synthesis of indole derivatives.[3–5]

While studying the reaction of the acetal of *N,N*-dimethylformamide (DMF) **3a** with **1** it was shown[3] that 1-acetyl-2-dimethylaminomethyleneindolin-3-one **2a** was formed. Under acidic conditions, this was hydrolysed to give 1-acetyl-2-formyl-3-hydroxyindole **4**. In the course of the present study it was established that, apart from the principal reaction to give **2a**, 2-dimethylaminomethylene-2*H*-pyrrolo[1,2-*a*]indole-3,9-dione **5a** was also obtained in 2% yield, m.p. 270–272 °C (MeOH–DMF), as a result of an unexpected side reaction between compounds **2a** and **3a** (Scheme 1). The structure of the tricyclic compound **5a** was proved by spectroscopic data.†‡

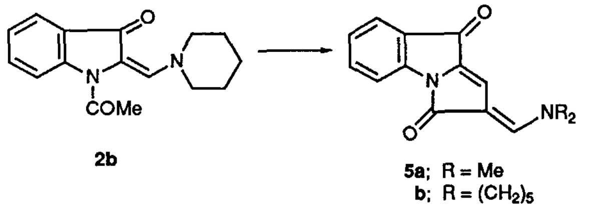
The pyrrolo[1,2-*a*]indole heterocyclic system is of interest because mitomycin, an antineoplastic antibiotic,[6] belongs to this series, and a number of compounds with similar structures possess antitumour,[7] antibacterial,[8] hypoglycaemic[9] and anti-allergenic[10] activity.

For this reason, we have developed a new preparative method for the synthesis of derivatives of this heterocyclic system and we have established a mechanism for the above-mentioned unexpected reaction. As the starting compound we used a more readily available compound than **2a**: 1-acetyl-2-piperidinomethyleneindolin-3-one **2b**.[3] Heating **2b** with an excess of acetal **3a** gave the tricyclic compound **5a** in 73% yield (Scheme 2). Heating **2b** with the diethylacetal **3b** of *N*-formylpiperidine afforded a 70% yield of the piperidinomethylene derivative **5b**, m.p. 234–235 °C (MeOH). The spectroscopic data of **5a,b** are similar.

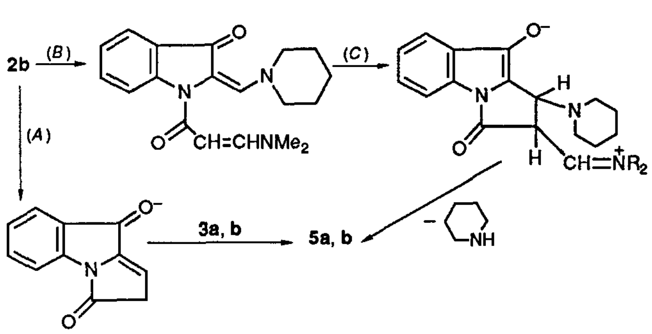
It is possible to suggest two routes for the formation of pyrrolo[1,2-*a*]indoles **5a,b** (Scheme 3). According to direction (*A*) the cyclization proceeds in the first stage, but according to direction (*B*, *C*) the condensation takes place first. It should be noted that both directions involve reactions that are unknown for amide acetals and enamines (*A*, *B*, *C*). Proof of course (*B*, *C*) as the true direction of the process was obtained by investigating the reaction between acetal **3a** and 1-acetyl-2-*p*-chlorophenylaminomethyleneindolin-3-one **6**.[3] The reaction of **3a** and **6** was carried out in refluxing benzene (Scheme 4) and the bis-enamino derivative 1-β-dimethylaminoacryloyl-2-*p*-chlorophenylaminomethyleneindolin-3-one **7** was isolated in 57% yield.§



Scheme 1 *Reagents*: i, $Me_2NCH(OEt)_2$, **3a**; ii, HCl–H_2O. Compound **5a** isolated by $CHCl_3$ extraction of the filtrate after separation of the aldehyde **4**. **5a** was purified by column (SiO_2) chromatography (eluents $CHCl_3$, DMF)

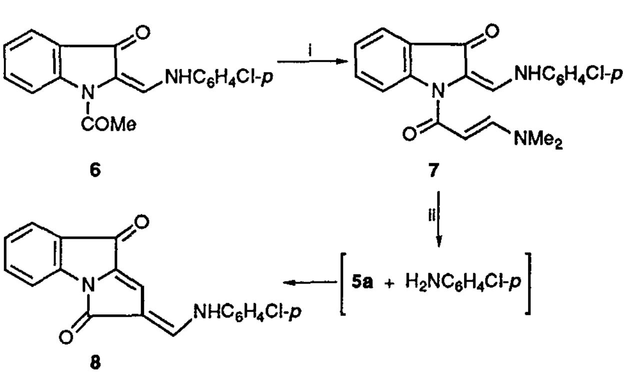


Scheme 2 *Reagents and conditions*: **3a** or **3b**, 115–120 °C, 60 min



Scheme 3

Refluxing a solution of **7** in xylene gave a mixture of



Scheme 4 *Reagents and conditions*: i, addition of benzene solution of **3a** to benzene solution of **6**, reflux for 30 min with distillation of EtOH, reflux for another 10 min; ii, xylene, b.p., 45 min

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† *Spectroscopic data* for **5a**: IR ν/cm^{-1} 1650, 1620; ^{1}H NMR ([$^2H_6$]-Me_2SO) δ 3.41 (s, 6H, NMe_2), 7.40 (s, 1H, 1-CH), 7.74 (s, 1H, α-CH), 7.12–7.20 and 7.55–7.69 (m, 4H, arom. protons); MS *m/z* 240 (M^+).

‡ All new compounds gave the expected IR, ^{1}H NMR and mass spectra and satisfactory elemental analyses.

§ *Spectroscopic data* for **7**: IR ν/cm^{-1} 3090, 1685, 1615, 1600; ^{1}H NMR ($CDCl_3$) δ 3.04 (6H, br s, NMe_2), 5.33 (1H, d, *CH*NMe$_2$), 7.76 (1H, d, COCH), 7.79 (1H, br s, *CH*NH), 9.00 (1H, br s, NH), 7.10–7.90 (8H, m, arom. protons); MS *m/z* 367 (M^+).

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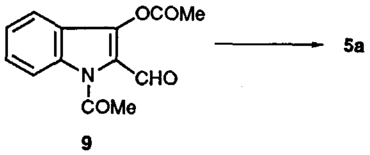

Scheme 5 *Reagents and conditions*: benzene, reflux, 30 min

pyrroloindole **5a** and 2-(*p*-chlorophenylaminomethylene)-2*H*-pyrrolo[1,2-*a*]indole-3,9-dione **8**. The latter was isolated from this mixture in 17% yield, m.p. 318–320 °C (DMF). Compound **8** was also obtained from **5a** by a transamination reaction with *p*-chloroaniline, in 86% yield.

Finally, it should be noted that this new reaction, involving the condensation of amide acetals at the methyl group of the *N*-acetyl substituent of enaminoindolin-3-one derivatives followed by cyclization of the intermediate enamino derivatives to give pyrroloindoles **5a**, **5b**, **8** may be conducted using various starting compounds. For example, heating 3-acetoxy-1-acetyl-2-formylindole **9** with acetal **3a** afforded **5a** although in a much poorer yield (6%) than that obtained using **2b**. The reaction was followed by *o*-deacylation (Scheme 5).

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