NOVEL APPLICATIONS OF THE "t-AMINO EFFECT" IN HETEROCYCLIC CHEMISTRY;
 SYNTHESIS OF 1-ALKYLINDOLES

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Abstract. Thermal rearrangement of 2-vinyl-1-(1-pyrrolidiny)benzenes varies with the leaving group ability of substituents in the vinyl moiety; compounds 3 having an OR group give 9-(alkoxymethyl)pyrrolo[1,2-a]indoles and compounds 6 (X = OAc, OTs or Cl) yield 1-alkylindoles.

Previously we have reported that 2-vinyl-*N,N*-dialkylanilines 1 can react in two different modes¹, depending on the position of electron-withdrawing groups in the vinyl moiety. A [1,6] hydrogen shift² occurs when R¹ = CN or R¹ = R² = COOCH₃ and a [1,5] hydrogen shift takes place when R² and R³ = CN or COOCH₃. The generation of a dipolar species is followed by ring closure to give e.g. pyrrolo[1,2-a]indoles and pyrrolo[1,2-a]quinolines, respectively. Both types of reaction represent the first examples of the "t-amino effect"³ of 2-vinyl-*N,N*-dialkylanilines. Moreover, the conversion of compounds 1 (R¹ = COOCH₃ or CN, R² = COOCH₃ or Ph, R³ = H and X = -) provides a simple route to pyrrolo[1,2-a]indoles¹, a heterocyclic system which constitutes the basic skeleton of the mitomycin anti-tumor antibiotics (2).

Essential for the bioactivity of the mitomycins is the urethane function at the 10-position. Therefore we have investigated the synthesis of compounds 3 and the thermal isomerization to 4 and 5 which have a (protected) hydroxymethyl group that can be converted into a urethane function⁴. The starting materials 3 were prepared using a procedure described by Cariou⁵ for the synthesis of α-(alkoxymethylene)benzeneacetonitrile derivatives. Reaction of 2-(1-pyrrolidiny)benzeneacetonitrile¹ with NaH in toluene at reflux temperature for 2 hours, followed by the addition of an excess of ethyl formate at 50-60 °C and additional reaction

for 4 hours at that temperature, led to the formation of the sodium salt of α -(hydroxymethylene)-2-(1-pyrrolidinyl)benzeneacetonitrile (**3a**) in a yield of 91% as a white solid. This enolate was subsequently reacted with several alkylating agents in DMF at room temperature for 2 hours. With dimethyl sulphate α -(methoxymethylene)-2-(1-pyrrolidinyl)benzeneacetonitrile (**3b**) was obtained as a 1:1 mixture of *E* and *Z* isomers⁶ in a yield of 86% [mp 88.5-89.0 °C; m/e 228.128 (M^+); IR (NaCl) 2200 cm^{-1} (CN); ^1H NMR (CDCl_3) δ 7.3-7.0 (m, 2H, Ar H), 6.97 and 6.89 (s, 1H, vinyl H), 6.9-6.6 (m, 2H, Ar H), 3.35-3.1 (m, 4H, NCH_2), 2.0-1.8 (m, 4H, CH_2); ^{13}C NMR (CDCl_3) δ 161.7 and 158.5 (d, =CH), 148.7 and 148.4 (s, C-2), 94.7 and 92.9 [s, =C(CN)], 50.8 and 50.5 (t, NCH_2)]. The other alkylation reactions were carried out with alkyl bromides to give the corresponding *n*-butyl- and benzylethers **3c** and **3d** in yields of 83% (oil) and 90% (oil), respectively⁷.

Compounds **3b-d** rearranged thermally to give the *cis*- and *trans*-tetrahydropyrrolo[1,2-*a*]indoles **4** and **5**, which were separated by column chromatography ($\text{SiO}_2/\text{CHCl}_3$); the results are given in the Table.

Table. Thermal rearrangement of **3b-d**.

Compd	R	Solvent	Temp (°C)	Time (days)	Compd (%)	
3b	CH_3	mesitylene	165	4	4a (13)	5a (48)
3b	CH_3	xylene	142	14	4a (22)	5a (26)
3c	$\text{n-C}_4\text{H}_9$	1-butanol	118	12	4b (73)	5b (9)
3c	$\text{n-C}_4\text{H}_9$	mesitylene	165	6	4b (12)	5b (56)
3d	CH_2Ph	mesitylene	165	3	4c (18)	5c (46)

By comparison of the spectral data of compound **4a** [mp 113.5-114.5 °C; IR (KBr) 2221 cm^{-1} (CN); m/e 228.125 (M^+); ^1H NMR (CDCl_3) δ 4.22 (dd, 1H, $J = 5.2$ and 10.0 Hz, NCH), 3.91 and 3.64 (AB q, 2H, $J = 9.4$ Hz, CH_2O), 3.48 (s, 3H, OCH_3), 3.5-2.9 (m, 2H, NCH_2); ^{13}C NMR (CDCl_3) δ 153.9 (s, C-4a), 73.6 (t, CH_2O), 73.4 (q, OCH_3), 59.5 (d, C-9a), 50.9 (t, NCH_2)] with those of the *cis*-2,3,9,9a-tetrahydro-9-(phenylmethyl)-1H-pyrrolo[1,2-*a*]indole-9-carbonitrile¹, the structure of which has been determined by X-ray analysis, compound **4a** was assigned to be *cis*-2,3,9,9a-tetrahydro-9-(methoxymethyl)-1H-pyrrolo[1,2-*a*]indole-9-carbonitrile⁸. Consequently **5a** was assigned the *trans* stereochemistry⁹ [mp 37.0-38.0 °C; IR (KBr) 2232 and 2208 cm^{-1} (CN); m/e 228.127 (M^+); ^1H NMR (CDCl_3) δ 4.1-3.8 (m, 1H, NCH), 3.64 and 3.47 (AB q, 2H, $J = 9.0$ Hz, CH_2O); ^{13}C NMR (CDCl_3) δ 120.2 (s, CN), 76.7 (t, OCH_2),

70.5 (q, OCH_3), 59.6 (d, C-9a)]. The differences between *cis* and *trans* isomers 4 and 5 are consistent with the results of earlier work^{1,2,10}; in general the NCH and CH_2R hydrogen atoms of the *cis* isomers absorb at lower field than those of the *trans* isomers and the CH_2R hydrogen atoms of the *cis* isomers exhibit a greater diastereotopic effect. The CH_2R carbon atoms of the *cis* isomers absorb at higher field than those of the *trans* isomers. Formation of the *cis* isomers 4 is preferred when the thermal rearrangement is carried out in polar solvent, whereas the formation of the *trans* isomers 5 is predominant in apolar solvents^{1,2,10}.

Reaction of compound 5a with at least 3 eq. of boron tribromide in CHCl_3 at room temperature for 2 hours gave the *trans*-9-(hydroxymethyl)-2,3,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]indole-9-carbonitrile 5d in a yield of 45% [mp 129.0-130.0 °C; m/e 214.112 (M^+); ^1H NMR (CDCl_3) δ 4.0-3.7 (m, 1H, NCH), 3.86 and 3.70 (AB q, 2H, J = 11.0 Hz, CH_2O), 3.45-3.0 (m, 2H, NCH_2), 2.86 (br s, 1H, OH); ^{13}C NMR (CDCl_3) δ 70.3 (d, C-9a), 67.6 (t, CH_2O), 52.2 (t, NCH_2)].

When the sodium enolate of 3a was reacted with acetyl chloride or *p*-toluenesulfonyl chloride in DMF at 50 °C for 2 hours we did not obtain the expected enol acetate or enol tosylate, respectively. In both cases we isolated 1-(4-chlorobutyl)-1*H*-indole-9-carbonitrile (9a)¹¹ [mp 48.0-48.5 °C; IR (NaCl) 2205 cm^{-1} (CN); m/e 232.073 (M^+); ^1H NMR (CDCl_3) δ 7.8-7.6 (m, 1H, Ar H), 7.57 (s, 1H, C-2 H), 7.5-7.1 (m, 3H, Ar H), 4.17 (t, 2H, J = 6.8 Hz, NCH_2), 3.51 (t, 2H, J = 6.1 Hz, CH_2Cl); ^{13}C NMR (CDCl_3) δ 135.2 (s, C-7a), 134.4 (d, C-2), 127.9 (s, C-3a), 115.7 (s, CN), 110.4 (d, C-7), 86.0 (s, C-3), 46.5 (t, NCH_2), 44.0 (t, CH_2Cl)] in yields of 65% and 60%, respectively. The structure was proven by X-ray analysis. Crystal data:

Figure. View of 9a.

$\text{C}_{13}\text{H}_{13}\text{ClN}_2$; monoclinic; space group $\text{P2}_1/\text{c}$, a = 13.075 (1), b = 11.844 (2), c = 8.103 (2) Å, β = 103.84 (8)°, Z = 4. Structure determination based on 1504 reflections (Cu K α radiation, graphite monochromator) with intensity greater than the standard deviation from counting statistics. The structure was solved by direct methods and refined with full matrix least-squares to a final R-factor of 7.7%. Parameters refined: scale factor, extinction parameter, positional parameters of all atoms, thermal parameters (isotropic for hydrogen atoms, anisotropic for others). All hydrogen atoms (except one) have been found from a difference Fourier synthesis; the hydrogen atoms found were

included in the refinement^{12a,b}. The structure of 9a (heavy atoms only) is shown in the Figure.

Treatment of the sodium enolate of 3a with acetic anhydride in DMF at 50 °C for

1 hour gave 1-[4-acetyloxy)butyl]-1H-indole-3-carbonitrile (**9b**) in a yield of 83% as an oil. The structure of **9b** was proven by comparison of the spectral data [IR (NaCl) 2216 cm^{-1} (CN); m/e 256.125 (M^+); ^1H NMR (CDCl_3) δ 4.20 (t, 2H, $J = 6.8\text{ Hz}$, NCH_2), 4.08 (t, 2H, $J = 6.1\text{ Hz}$, CH_2OAc); ^{13}C NMR (CDCl_3) δ 170.8 (s, C=O), 63.4 (t, CH_2OAc), 46.4 (t, NCH_2), 20.8 (q, CH_3)] with those of **9a**.

We can explain the rearrangement of **6** to **9** in terms of an intramolecular Michael addition of the *t*-amino group to the electron-deficient double bond, followed by elimination of the leaving group, leading to the spiro compound **8**. Finally attack of **8** by the stronger nucleophile gives the 1-alkylindole derivatives **9**. This reaction represents the third possible reaction pathway of 2-vinyl-*N,N*-dialkylanilines.

Scheme

It cannot be excluded that an intermediate comparable to **7** is formed in all the reactions of 2-vinyl-*N,N*-dialkylanilines¹. In most cases the Michael addition cannot be followed by a subsequent elimination reaction, which renders this addition reversible. However, when a good leaving group is present in the β -position of the vinyl moiety, elimination of this leaving group makes the equilibrium shift to the right. A similar reaction has been described by Meth-Cohn and Suschitzky *viz.* the formation of 1,2-substituted benzimidazoles from *N,N*-dialkylanilines having an imino moiety bearing a good leaving group at the 2-position³.

References and notes

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- Satisfactory elemental analyses were obtained for all new crystalline compounds ($\text{C, H, N} \pm 0.4\%$).
- Mixture of *E* and *Z* isomers in a 1:1 ratio.
- Compounds **4b** (mp $46.5\text{--}47.5^\circ\text{C}$) and **4c** [oil; ^1H NMR (CDCl_3) δ 4.73 and 4.56 (AB q, 2H, $J = 12.7\text{ Hz}$, OCH_2Ph)] exhibit similar spectral data as **4a**.
- Compounds **5b** (oil) and **5c** (oil) exhibit similar spectral data as **5a**.
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- Compound **9a** was also formed as the major product in the reaction of **3b** in acetonitrile in the presence of ZnCl_2 , presumably substitution of the methoxy group by chloride has taken place under influence of ZnCl_2 .
- (a) The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK. Any request should be accompanied by the full literature citation for this communication. (b) Supplementary data available: a list of observed and calculated structure factors. See Announcement to Authors, *Tetrahedron Lett.* **24**, 5154 (1983).

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