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

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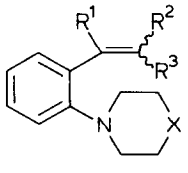
Abstract. *Thermal rearrangement of 2-vinyl-1-(1-pyrrolidinyl)benzenes varies with the leaving group ability of substituents in the vinyl moiety; compounds 3 having an OR group give 9-(alkoxymethyl)pyrrolo[1,2-a]indoles and compounds 6 (X = OAc, OTs or Cl) yield 1-alkylindoles.*

Previously we have reported that 2-vinyl-*N*,*N*-dialkylanilines 1 can react in two different modes[1], depending on the position of electron-withdrawing groups in the vinyl moiety. A [1,6] hydrogen shift[2] occurs when R^1 = CN or R^1 = R^2 = $COOCH_3$ and a [1,5] hydrogen shift takes place when R^2 and R^3 = CN or $COOCH_3$. 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 (R^1 = $COOCH_3$ or CN, R^2 = $COOCH_3$ or Ph, R^3 = H and X = -) provides a simple route to pyrrolo[1,2-*a*]indoles[1], 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 function[4]. The starting materials 3 were prepared using a procedure described by Cariou[5] for the synthesis of α-(alkoxymethylene)benzeneacetonitrile derivatives. Reaction of 2-(1-pyrrolidinyl)benzeneacetonitrile[1] 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



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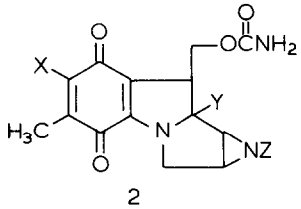

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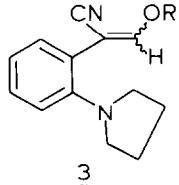
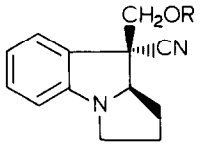


3

a. R = H
b. R = CH_3
c. R = n-C_4H_9
d. R = CH_2Ph

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* isomers[6] 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), respectively[7].

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 (SiO_2/$CHCl_3$); the results are given in the Table.



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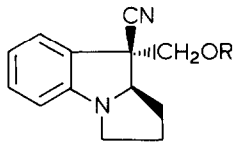


5

a. R = CH_3
b. R = n-C_4H_9
c. R = CH_2Ph
d. R = H

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	n-C_4H_9	1-butanol	118	12	4b (73)	5b (9)
3c	n-C_4H_9	mesitylene	165	6	4b (12)	5b (56)
3d	CH_2Ph	mesitylene	165	3	4c (18)	5c (46)

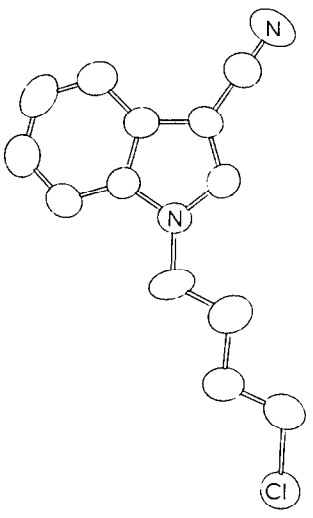
By comparison of the spectral data of compound 4a [mp 113.5-114.5 °C; IR (KBr) 2221 cm^{-1} (CN); *m/e* 228.125 (M^+); ^1H NMR ($CDCl_3$) δ 4.22 (dd, 1H, *J* = 5.2 and 10.0 Hz, NCH), 3.91 and 3.64 (AB q, 2H, *J* = 9.4 Hz, CH_2O), 3.48 (s, 3H, OCH_3), 3.5-2.9 (m, 2H, NCH_2); ^{13}C NMR ($CDCl_3$) δ 153.9 (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)-1*H*-pyrrolo[1,2-*a*]indole-9-carbonitrile[1], 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)-1*H*-pyrrolo[1,2-*a*]indole-9-carbonitrile[8]. Consequently 5a was assigned the trans stereochemistry[9] [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)-2,3,9,9a-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^+); ^{1}H 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^+); ^{1}H 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: $C_{13}H_{13}ClN_2$; monoclinic; space group $P2_1/c$, 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 Kα 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.

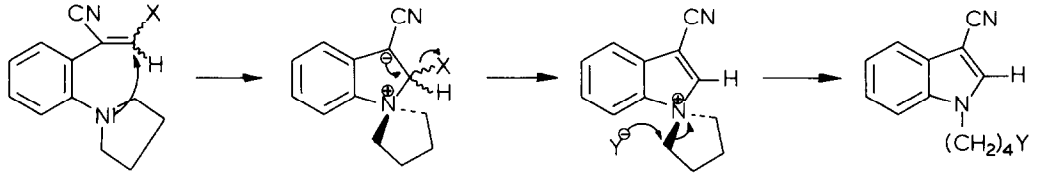
Figure. View of 9a.



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

1 hour gave 1-[4-acetyloxy)butyl]-1*H*-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 Hz, NCH_2), 4.08 (t, 2H, *J* = 6.1 Hz, CH_2OAc); ^{13}C NMR ($CDCl_3$) δ 170.8 (s, C=O), 63.4 (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.



6 X=OAc,OTs,Cl 7 8 9a. Y=Cl b. Y=OAc

Scheme

It cannot be excluded that an intermediate comparable to 7 is formed in all the reactions of 2-vinyl-*N*,*N*-dialkylanilines[1]. 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-position[3].

References and notes

1. W. Verboom, D.N. Reinhoudt, R. Visser and S. Harkema, *J. Org. Chem.* in the press.
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6. Satisfactory elemental analyses were obtained for all new crystalline compounds (C,H,N ± 0.4%).
7. Mixture of *E* and *Z* isomers in a 1:1 ratio.
8. Compounds 4b (mp 46.5-47.5 °C) and 4c [oil; ^1H NMR ($CDCl_3$) δ 4.73 and 4.56 (AB q, 2H, *J* = 12.7 Hz, OCH_2Ph)] exhibit similar spectral data as 4a.
9. Compounds 5b (oil) and 5c (oil) exhibit similar spectral data as 5a.
10. D.N. Reinhoudt, J. Geevers, W.P. Trompenaars, S. Harkema and G.J. van Hummel, *J. Org. Chem.* 46, 424 (1981); W. Verboom, G.W. Visser, W.P. Trompenaars, D.N. Reinhoudt, S. Harkema and G.J. van Hummel, *Tetrahedron* 37, 3525 (1981); G.W. Visser, W. Verboom, W.P. Trompenaars and D.N. Reinhoudt, *Tetrahedron Lett.* 23, 1217 (1982).
11. 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 $ZnCl_2$.
12. (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 IEW, 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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