New Reactions of Deoxyvasicinone. Part 2

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Deoxyvasicinone (**1**) was shown to react with chloral, ethyl chloroacetate and chlorinated acetyl chlorides. The reactions between **1** and both acetic anhydride and vinyl acetate are reported and the structures of the products from these two reactions elucidated by pmr spectroscopy.

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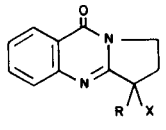
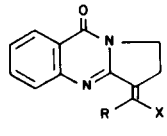
In an earlier paper [1] we reported that deoxyvasicinone [1] reacts readily with electrophiles at the 3 position of the pyrrolo ring probably through the intermediacy of an enamine. We now wish to report several new reactions of **1** with electrophiles which lead to derivatives of potential value in the synthesis of novel alkaloids.



1, R = X = H
2, R = $CH(OH)CCl_3$, X = H
6, R = CH_2CO_2Et, X = H



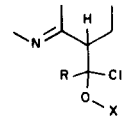
3, R = CH_2Cl, X = Cl
4, R = $CHCl_2$, X = Cl
5, R = OH, X = CCl_3
7, R = Me, X = OAc
8, R = OAc, X = Me
9, R = H, X = Me
10, R = Me, X = H

The first reaction studied was that between **1** and chloral hydrate [2]. Although it has been established that **1** will not undergo condensation with aliphatic aldehydes, the reaction of 2-methylpyridine with chloral hydrate has been known for almost one hundred years [3]. More recently Taylor [4] has shown that pyrrolo[1,2-*a*]quinazolines also undergo condensation with chloral to yield adducts. When **1** was heated gently with excess chloral hydrate a thick dark red paste was produced from which **2** was isolated. This result led us to investigate the reaction of **1** with other reagents possessing halogen atoms α to a carbonyl group. When **1** was heated in excess chloroacetyl chloride or dichloroacetyl chloride the chloroethylidene derivatives **3** and **4** resulted. However when **1** was heated with trichloroacetyl chloride the enol **5** was the only isolable product. We believe that both **3** and **4** exist in the *E* configuration and that there is a strong hydrogen bond between the acidic chloromethyl (or dichloromethyl) protons and the sp^2 nitrogen atom (figure 1). This hypothesis is supported

Figure 1

X = H or Cl

Figure 2



X = H or $COCH_nCl_{(3-n)}$

R = $CH_nCl_{(3-n)}$

by the low δ value for these protons (see experimental). It is also likely that an unfavourable dipole-dipole interaction between this nitrogen atom and chlorine in a *Z* configuration may be a contributing factor for the exclusive stereochemical course of these reactions. In all these reactions an intermediate of the type shown in figure 2 is almost certainly involved. In the case of trichloroacetyl chloride steric factors will compel the trichloromethyl group to adopt a *trans* position and since a *Z* chlorine atom is probably undesirable, elimination of hydrogen chloride is the preferred route in the decomposition of the intermediate. We are unable to state whether the initial product from the reaction between **1** and trichloracetyl chloride is the enol **5** or a labile enol trichloroacetate.

When **1** was heated with an excess of ethyl chloroacetate, the ester **6** was produced in low yield.

Reaction of **1** (or its hydrochloride) with excess acetic anhydride under reflux produces two products which, after purification by column chromatography, were shown to be the isomeric enol acetates **7** and **8**. The major isomer **7** was assigned the *E* configuration from its pmr spectrum. In the pmr spectrum of **7** the acetate methyl group appears at δ 2.18 and the alkene methyl group at δ 2.60 whilst in the pmr spectrum of **8** the relative positions are δ 2.38 and δ 2.06 respectively. In the spectrum of both **7** and **8** the alkene methyl group is complex due to homoallylic coupling to the protons of C-2 in the pyrrolo ring. No diacetyl compounds of the type reported by Taylor [4] were isolated from these reactions.

Condensation also occurred when **1** was heated with vinyl acetate and triethylamine in a sealed tube. Two products were obtained and these were separated by chromatography and shown to be the isomeric ethylidene derivatives **9** and **10**. Again it was possible to assign the relative configuration by examination of their pmr spectra. In the

spectrum of the major isomer **9** the alkene methyl group appears at δ 1.80 and the olefin proton δ 6.5-7.1 which is consistent with an *E* configuration. In the spectrum of the minor isomer the alkene methyl group appears at δ 2.38 and the alkene proton at δ 6.1 which is compatible with a *Z* configuration. Both the alkene hydrogen and methyl group are allylically and homoallylically coupled respectively to the protons on C-2 of the pyrrolo ring. Spin-spin decoupling experiments confirmed these observations.

We are continuing to investigate the chemistry of deoxyvasicinone and related compounds and further results in this area will be reported in the near future.

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were recorded for potassium bromide on a Perkin-Elmer 397 spectrometer and pmr spectra on at 60 MHz on a Jeol PMX 60 SI spectrometer and at 90 MHz on a Jeol FX 90Q spectrometer. Mass spectra were recorded at 70ev on an AEI MS 9 spectrometer. Thin layer chromatography was performed on aluminium backed plates of silica gel (7 × 5 cm) cut from sheets (Merck DC-Alufolein, Kieselgel 60 F_{254}) in triethylamine/ethyl acetate (1:9).

Condensation Between **1** and Chloral Hydrate.

Chloral hydrate (5.34 g) and **1** (5 g) were intimately mixed and heated gently until the resulting clear homogeneous solution darkened. The mixture was cooled and the thick red paste treated with chloroform/ether to yield a white crystalline solid. Recrystallisation from ether gave white needles of pure **2** (3.7 g, 41%) mp >300° dec, Rf 0.70; ir (potassium bromide): 3700-3100 (broad), 1660, 1620 cm^{-1}; pmr (60 MHz, D_6-DMSO): 8.06 (1H, d), 7.8-7.3 (3H, complex), 7.14 (1H, d, J = 7 Hz, exchangeable), 4.90 (1H, d, J = 7 Hz), 4.4-3.6 (3H complex), 2.9-2.1 (2H, complex); ms: m/e 334, 332 (both m^+).

Anal. Calcd. for $C_{13}H_{11}Cl_3N_2O$: C, 46.8; H, 3.3; Cl, 31.9; N, 8.1. Found: C, 46.5; H, 3.4; Cl, 31.9; N, 8.1.

Condensation of **1** With Acid Chlorides.

(a) Chloroacetyl Chloride.

A mixture of **1** (1 g) and chloroacetyl chloride (10 ml) was heated under reflux for 3½ hours. The mixture darkened considerably during the reaction and on cooling the excess chloroacetyl chloride was removed *in vacuo*. The residue crystallized from ethyl acetate and the crude product was decolourised and recrystallised from ethyl acetate to yield pure **3** (820 mg, 57%) mp 211.5-212.5°, Rf 0.88; ir (potassium bromide): 1670, 1590 cm^{-1}; pmr (90 MHz, D_6-DMSO): 8.14 (1H, complex), 7.9-7.4 (3H, complex), 5.49 (2H, 5, J = 1 Hz), 4.08 (2H, q), 3.05 (2H, quintet); ms: m/e 284, 282, 280 (all m^+).

Anal. Calcd. for $C_{13}H_{16}Cl_2N_2O$: C, 55.5; H, 3.6; N, 10.0. Found: C, 55.7; H, 3.6; N, 9.95.

(b) Dichloroacetyl Chloride.

A mixture of **1** (1 g) and dichloroacetyl chloride (10 ml) was heated gently under reflux for 1½ hours. The mixture was cooled, excess acid chloride removed *in vacuo* and the residue chromatographed on silica gel (24 g). Elution with light petroleum:ether (1:1) gave an orange oil which crystallised from ether. Recrystallisation and decolourisation gave pure **4** (200 mg, 12%) mp 189-190.5°, Rf 0.88; ir (potassium bromide): 1685, 1600 cm^{-1}; pmr (90 MHz, D_6-DMSO): 9.27 (1H, s), 8.20 (1H, dd), 8.0-7.4 (3H, complex), 4.10 (2H, t, J = 8 Hz), 3.09 (2H, t, J = 8 Hz); ms: m/e 318, 316, 314 (all m^+).

Anal. Calcd. for $C_{13}H_9Cl_3N_2O$: C, 49.4; H, 2.8; N, 8.9. Found: C, 49.4; H, 2.8; N, 9.0.

(c) Trichloroacetyl Chloride.

A mixture of **1** (2.02 g) and trichloracetyl chloride (10 ml) was heated under reflux for 1½ hours. The mixture was cooled, excess trichloroacetyl chloride removed *in vacuo* and the residue chromatographed on silica gel (60 g). Elution with dichloromethane:ethyl acetate (1:1) gave a brown semi solid mass. Decolourisation and recrystallisation gave pale yellow needles of pure **5** (310 mg, 9%) mp >235° dec, Rf 0.55; ir (potassium bromide): 3600-3100 (weak, broad), 1690, 1640, 1540 cm^{-1}; pmr (90 MHz, D_6-DMSO): 11.84 (1H, broad S, exchangeable), 8.1-7.2 (4H, complex), 4.16 (2H, q), 3.19 (2H, q); ms: m/e 334, 332, 330 (all m^+).

Anal. Calcd. for $C_{13}H_9Cl_3N_2O_3$: C, 47.1; H, 2.7; N, 8.5; Cl, 32.1. Found: C, 47.1; H, 2.4; N, 8.5; Cl 32.5.

Condensation of **1** With Ethyl Chloroacetate.

Ethyl chloroacetate (10 ml) and **1** (1 g) were heated under reflux for 7 hours, cooled and the excess ethyl chloroacetate removed *in vacuo*. The residue was chromatographed on silica gel (30 g). Elution with ether gave an orange syrup which rapidly crystallised. Decolourisation and recrystallisation gave the pure ester **6** (170 mg, 11%) mp 92°, Rf 0.75; ir (potassium bromide): 1730, 1670, 1620, 1610 cm^{-1}; pmr (60 MHz, deuteriochloroform): 7.82 (1H, d, J = 7 Hz), 7.4-6.8 (3H, complex), 4.2-1.3 (9H, complex), 0.98 (3H, t); ms: m/e 272 (m^+).

Anal. Calcd. for $C_{15}H_{16}N_2O_3$: C, 66.2; H, 5.9; N, 10.3. Found: C, 66.2; H, 5.8; N, 10.3.

Condensation of **1** With Acetic Anhydride.

A mixture of **1** (2 g) and acetic anhydride (5 ml) was heated under reflux for 12 hours. The mixture was cooled, solvents removed *in vacuo* and the residue chromatographed on silica gel (70 g). Elution with light petroleum:ether (6:4) gave the *E* enol acetate **7** which was recrystallised from ether/ethyl acetate to yield pure **7** as colourless needles (550 mg, 19%) mp 177°, Rf 0.84; ir (potassium bromide): 1750, 1670, 1600 cm^{-1}; pmr (60 MHz, deuteriochloroform): 8.16 (1H, d), 7.8-7.1 (3H, complex), 4.02 (3H, t, J = 7 Hz), 2.76 (2H, doublet of triplets, J = 7 Hz and 1.5 Hz), 2.60 (3H, d, J = 1.5 Hz), 2.18 (3H, s); ms: m/e 270 (m^+).

Anal. Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.7; H, 5.2; N, 10.4. Found: C, 66.8; H, 5.1; N, 10.3.

Further elution gave the *Z* isomer **8** as a syrup which rapidly crystallised. Recrystallisation gave pure **8** as fine colourless needles (100 mg, 4%) mp 184.5-185.5°, Rf 0.74; ir (potassium bromide): 1760, 1680, 1600 cm^{-1}; pmr (60 MHz deuteriochloroform): 8.16 (1H, d), 7.8-7.1 (3H complex), 4.11 (2H, t, J = 7 Hz), 2.9 (2H, doublet of triplets, J = 7 and 1.8 Hz), 2.38 (3H, s), 2.06 (3H, d, J = 1.8 Hz); ms: m/e 270 (m^+).

Anal. Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.7; H, 5.2; N, 10.4. Found: C, 66.4; H, 5.3; N, 10.3.

Condensation Between Deoxyvasicinone Hydrochloride and Acetic Anhydride.

A mixture of deoxyvasicinone hydrochloride (6.1 g) and acetic anhydride (15 ml) was heated under reflux for 72 hours. The solvents were removed *in vacuo* and the residue extracted with ethyl acetate. The concentrated extracts were purified by preparative tlc on 12 plates (Merck Kieselgel 60 F_{254}, 20 × 20 cm, thickness 2 mm) using ethyl acetate:triethylamine (9:1) to yield the pure *E* acetate **7** (1.21 g, 17%) and the pure *Z* isomer **8** (550 mg, 8%). Both products were identical in all respects to the compounds described above.

Condensation Between **1** and Vinyl Acetate.

A mixture of **1** (5 g), triethylamine (0.5 ml) and vinyl acetate (12 ml) was heated at 150° for 18 hours in a sealed tube during which time the mixture darkened considerably. The cooled tube was opened, volatiles removed *in vacuo* and the residue chromatographed on silica gel (150 g). Elution with ethyl acetate:light petroleum (1:1) gave **10** as a white solid. Recrystallisation from ethyl acetate/light petroleum gave pure **10** as fine white crystals (350 mg, 6%) mp 148-150° dec, Rf 0.80; ir (potassium bromide): 1675, 1600 cm^{-1}; pmr (60 MHz, deuteriochloroform): 8.08 (1H, d), 7.7-7.1 (3H, complex), 6.1 (1H, complex), 4.05 (2H, t), 2.86 (2H, complex), 2.38 (3H, doublet of triplets). Double irradiation at δ 6.1 causes the signal at δ 2.38 to reduce to a triplet and the signal at δ 2.86 to simplify;

ms: m/e 212 ($m^{+\cdot}$).

Anal. Calcd. for $C_{13}H_{12}N_2O$: C, 73.6; H, 5.7; N, 13.2. Found: C, 73.3; H, 5.65; N, 13.0.

Further elution with the same solvent gave **9** as fine needles. Recrystallisation from ethyl acetate/light petroleum gave pure **9** (570 mg, 10%) mp 169-170°, Rf 0.75; ir (potassium bromide): 1665, 1600 cm^{-1}; pmr (60 MHz, deuteriochloroform): 8.10 (1H, d), 7.8-7.1 (3H, complex), 7.1-6.5 (1H, complex), 4.04 (2H, t), 2.70 (2H, complex), 1.8 (3H, complex). Double irradiation of the signal at δ 1.8 cause the signal at δ 2.70 to simplify and the signal at δ 6.5-7.1 to collapse to a singlet with a slight shoulder at δ 6.82; ms: m/e 212 ($m^{+\cdot}$).

Anal. Calcd. for $C_{13}H_{12}N_2O$: C, 73.6; H, 5.7; N, 13.2. Found: C, 73.6; H, 5.7; N, 13.2.

REFERENCES AND NOTES

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[2] We are indebted to Prof. Dr. W. Schroth of the Martin Luther University, Halle, DDR, for this suggestion.

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[4] E. C. Taylor and Y. Shvo, *J. Org. Chem.*, **33**, 1719 (1968).