New Reactions of Deoxyvasicinone

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Deoxyvasicinone **1** was shown to react at the 3 position of the pyrrolidine ring with chloroformate esters and benzoyl chloride. Deuterium exchange at this site is also reported.

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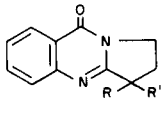
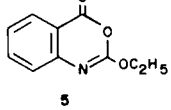
Several authors (1) have reported that deoxyvasicinone (**1**) and related fused quinazolines undergo reaction at the C−3 position in the pyrrolidine ring. The protons in this position bear a strong resemblance to the protons of the methyl group in 2-picoline and quinaldine (2), (3) but the fact that **1** condenses with aromatic aldehydes without catalysis indicate that they are much more reactive. However little use (1d) has been made of these reactions to prepare derivatives which could function as intermediates in the synthesis of novel alkaloids. The aim of this note is to report our results on the reaction of **1** with electrophiles. The reactions proceed *via* tautomerism of the C−3 acid hydrogen with subsequent generation of an enamine.

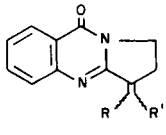
When **1** was heated with deuterium oxide at 150° (sealed tube) the product obtained was the 3,3-dideutero derivative **2**. The ease with which this reaction occured lead us to study the interaction of **1** with chloroformic esters but no reaction was evident in a variety of solvent/base mixtures. However in neat ethyl chloroformate using **1** both as reactant and base reaction did occur. The product was dependent upon the reaction time. Short reaction times (8-10) hours) favoured the formation of **3** whilst longer reaction times gave **4** and **5**. In both cases the major reaction product was the hydrochloride of **1**. The structures of **3** and **4** were established from their ^{13}C nmr spectra. The formation of **5** can be rationalised on the basis of (4 + 2) π cycloaddition of some intermediate iminoketene of the type previously postulated (4). although the actual machanism for its generation is not yet known.



1, R = R' = H
2, R = R' = D
4, R = R' = CO_2Et
6, R = R' = CO_2Bu
7, R = H, R' = CO_2Et



5



3, R = EtO, R' = OCO_2Et
8, R = Cl, R' = Ph

Similarly **1** reacted with butyl chloroformate to yield **6**. Minor products from this reaction were not investigated.

Conversion of **3** into **4** was easily accomplished by heating the former with ethyl chloroformate and the hydrochloride of **1**. When **4** was treated with ethanolic ammonia the expected diamide was not isolated, instead the reaction product was the monoester **7**.

Condensation also occurred when **1** or its hydrochloride was heated in benzoyl chloride. The major reaction product was the α-chlorobenzylidene derivative **8**.

We are currently evaluating the synthetic potential of derivatives **4** and **7** and investigating the reaction of **1** with other electrophiles.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded on a Perkin Elmer 397 spectrometer. The pmr and ^{13}C nmr spectra were recorded in deuteriochloroform solution using tetramethylsilane as internal standard on a Jeol JMN PMX60S1 and Brucker WP 80 DS spectrometers at 60 MHz and 20.15 MHz respectively. Mass spectra were recorded on an AEI MS-9 spectrometer at 70eV.

3,3-Dideutero-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-9-one (**2**).

Deuterium oxide (5 ml) and **1** (100 mg) were heated in a sealed tube at 150° for 15 hours. The contents were removed and concentrated *in vacuo* to yield a white solid (180 mg). Recrystallisation from ethaer gave pure **2** (160 mg, 79%), mp 109.5-110°; ir (potassium bromide): 1675, 1620 cm^{-1}; pmr: δ 2.20 (2H, t), 4.07 (2H, t), 7.0-7.9 (3H, complex), 8.13 (1H, d, H = 8 Hz); ms: m/e 188 (100%) $M^{+\cdot}$.

Anal. Calcd. for $C_{11}H_8D_2N_2O$: C, 70.2; H, 6.4; N, 14.9. Found: C, 70.0; H, 6.4; N, 14.8.

Reaction Between **1** and Ethyl Chloroformate.

(a) Ethyl chloroformate (25 ml) and **1** (21.5 g) were heated under reflux until a thick paste was produced (*ca* 1 hour). Further quantities of ethyl chloroformate (4 × 10 ml) were added at ½ hour intervals and the paste heated at 110-120° for a further 5 hours. The mixture was diluted with ethyl acetate (100 ml) and filtered to remove the hydrochloride of **1** (14.1 g). After decolourisation and concentration the syrupy residue was crystallised from ether to yield **3** (4.35 g). Recrystallisation from ethyl acetate/ether gave pure **3** (4.06 g, 11%), mp 100-101°; ir (potassium bromide): 2990, 2940, 2800, 1750, 1690, 1625 cm^{-1}; pmr: δ 1.20 (6H, t), 2.83 (2H, complex), 4.10 (6H, complex), 6.95-8.20 (4H, complex); ^{13}C nmr: δ 13.92, 14.41, 25.79, 43.34, 60.03, 64.03, 98.81, 119.73, 120.00, 125.09, 127.31, 133.70, 138.74, 143.29, 152.07, 159.07, 164.42; ms: m/e 330 (23%) $M^{+\cdot}$.

Anal. Calcd. for $C_{17}H_{18}N_2O_5$: C, 61.8; H, 5.45; N, 8.5. Found: C, 62.1; H, 5.5; N, 8.3.

(b) Ethyl chloroformate (50 ml) and **1** (10.71 g) were heated under reflux until a thick paste was formed. The paste was maintained at 100-120° for 1 hour, ethyl chloroformate (50 ml) added and the mixture

heated under reflux until a paste was again produced and the paste treated as above. Ethyl acetate (100 ml) was added, the mixture filtered and the hydrochloride of **1** obtained reconverted to **1** with dilute sodium hydroxide solution. The regenerated **1** and the filtrate were combined, the solution concentrated *in vacuo* and the above cycle repeated another four times. Ethyl acetate (100 ml) was added and the mixture filtered to remove the hydrochloride of **1** (2.5 g). Decolourisation and concentration of the filtrate gave a colourless syrup which rapidly crystallised in ether. Recrystallisation of the product from ether/dichloromethane gave colourless prisms of pure (**4**) (6.18 g, 33%), mp 119-120°; ir (potassium bromide): 2990, 2970, 2800, 1730, 1680, 1625, 1610 cm^{-1}; pmr: δ 1.38 (6H, t), 3.00 (2H, t), 4.50 (6H, complex), 7.40-8.05 (3H, complex), 8.42 (1H, d, J = 8 Hz); ^{13}C nmr: δ 14.00, 30.07, 43.87, 62.88, 64.95, 121.03, 126.09, 127.08, 128.06, 134.10, 149.00, 153.73, 160.53, 166.91; ms: m/e 330 (19%) $M^{+\cdot}$.

Anal. Calcd. for $C_{17}H_{18}N_2O_5$: C, 61.8, H, 5.45; N, 8.5. Found: C, 61.7; H, 5.6; N, 8.4.

The mother liquors from the crystallisation were concentrated and chromatographed on silica gel. Elution with light petroleum:ether (3:2) gave 2-ethoxy-4*H*-3,1-benzoxazin-4-one (**5**) (0.75 g) as a pink solid. Recrystallisation from the above solvent mixture gave pure **5** as colourless leaflets (0.55 g 5%), mp 92° (5); (potassium bromide): 1760, 1635, 1610 cm^{-1}; pmr: δ 1.48 (3H, t), 4.59 (2H, q), 7.2-8.0 (3H, complex), 8.25 (1H, d, J = 8 Hz); ms: m/e 191 (60%) $M^{+\cdot}$.

Anal. Calcd. for $C_{10}H_9NO_3$: C, 62.8; H, 4.7; N, 7.3. Found: C, 63.1; H, 4.6; N, 7.0.

3,3-Dibutoxycarbonyl-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-9-one (**6**).

Butyl chloroformate (50 ml) and **1** (8.5 g) were heated under reflux for 7 days. The mixture was diluted with ethyl acetate (100 ml), filtered to remove the hydrochloride of **1** (4.86 g), and the filtrate concentrated to yield a colourless syrup. The syrup was chromatographed on silica gel. Elution with light petroleum:ether (3:2) gave **6** (3.2 g) as a colourless syrup. Distillation (Kugelrohr) gave the pure title compound (2.6 g, 15%), bp 245°/4mm Hg; ir (film sodium chloride): 2950, 2925, 2820, 1730, 1680, 1625, 1610 cm^{-1}; pmr: δ 0.8-2.1 (14 H, complex), 2.93 (2H, t), 4.26 (6H, complex q), 7.3-7.9 (3H, complex), 8.30 (1H, d, J = 8 Hz); ms: m/e 386 (19%) $M^{+\cdot}$.

Anal. Calcd. for $C_{21}H_{26}N_2O_5$: C, 65.3; H, 6.7; N, 7.25. Found: C, 65.0; H, 6.85; N, 7.0.

Conversion of **3** Into **4**.

Ethyl chloroformate (10 ml), the hydrochloride of **1** (0.25 g) and **3** (0.67 g) were heated under reflux until at thick paste was produced. The paste was maintained at 120° for 8 hours, cooled and ethyl acetate (20 ml) added. The mixture was filtered and the filtrate concentrated to yield a solid. Recrystallisation from ether/dichloromethane gave **4** (0.45 g), mp 118-119°, identical in all respects to an authentic sample.

3-Ethoxycarbonyl-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-9-one (**7**).

A solution of **4** (0.47 g) in ethanol (25 ml) presaturated with dry ammonia gas was allowed to stand overnight. The solvents were removed *in vacuo* and the residue crystallised from ether. Recrystallisation from ether gave the pure monoester **6** (0.21 g 62%), mp 91-92°; ir (potassium bromide): 2975, 2900, 1735, 1685, 1620 cm^{-1}; pmr: δ 1.29 (3H, t), 260 (2H, t), 4.23 (5H, complex), 7.3-7.9 (3H, complex), 8.30 (1H, d, J = 8 Hz); ms: m/e 258 (23%).

Anal. Calcd. for $C_{14}H_{14}N_2O_3$: C, 65.1; H, 5.4; N, 10.85. Found: C, 64.8; H, 5.4; N, 10.6.

Reaction Between **1** and Benzoyl Chloride.

(a) Benzoyl chloride (12 ml) and **1** (1,4 g) were heated under reflux for 1½hours. The mixture was cooled, flooded with light petroleum and the insoluble material crystallised from ether to yield a cream solid (1.12 g). Recrystallisation from ethyl acetate gave the pure α-chlorobenzylidene derivative **8** (1.01 g 43%), mp 162-163°; ir (potassium bromide): 1675, 1610, 1590 cm^{-1}; pmr: δ 3.10 (2H, t), 4.17 (2H, t), 7.0-7.9 (8H, complex), 8.19 (1H, dd, J = 2 and 8 Hz), ms: m/e 310 (27%) and 308 (75%) both $M^{+\cdot}$.

Anal. Calcd. for $C_{18}H_{13}ClN_2O$: C, 70.0; H, 4.2; Cl, 11.5; N, 9.1. Found: C, 70.0; H, 4.0; Cl, 11.3; N, 9.0.

(b) Benzoyl chloride (5 ml) and the hydrochloride of **1** (0.51 g) were heated under reflux for 5 hours. The mixture was treated as above to yield pure **8** (0.21 g, 29%), mp 162-163°.

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