New Reactions of Deoxyvasicinone. Part 6

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Several acylated derivatives of deoxyvasicinone **1** and its analogues were shown to exist as enols. The 3-hydroxymethyl derivative of **1** was shown to undergo rapid dehydration and products derived from an intermediate 3-methylene compound were obtained. Novel oxazepino analogues of **1** are reported.

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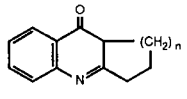
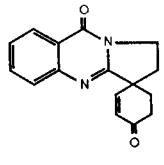
In earlier papers [1-5] we have described the synthesis and some reactions of **1** and its analogues. More recently we have reported the preparation of analogues of **1** in which the benzene ring is replaced by either a pyridine or a pyrazine ring [6]. We now wish to report some new reactions of **1** and some of its analogues, and the synthesis of novel oxazepinoquinazolinones.

Our initial target compound was the 3-hydroxymethyl derivative **2**. One obvious starting point is the known 3-hydroxymethylene derivative **3**, easily accessible by Vilsmier-Haack formylation of **1** [7]. Treatment of **1** with dimethylformamide and phosphorus oxychloride as described by Shakhidoyatov [7] gave the desired intermediate **3** in excellent yield. The enol structure of this formyl derivative was confirmed by infrared spectroscopy and it is probable that stabilisation of this tautomer is achieved by intramolecular hydrogen bonding between the sp^2 nitrogen atom and the hydroxyl hydrogen atom. We have previously reported that the 3-benzoyl derivative also exists as its enol tautomer **4** [3], [8] and consequently



	n	R	X
1	1	H	H
2	1	CH_2OH	H
7	2	H	H
8	3	H	H
13	1	Me-C=N-NHPh	H
14	1	Me	H
17	1	CH_2OH	CH_2OH
18	1	CH_2OH	CH_2OEt
19	1	CH_2OAc	CH_2NMe_2



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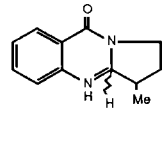

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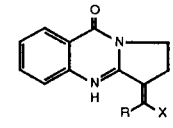
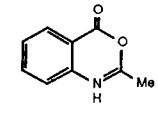


	n	R	X
3	1	HO	H
4	1	HO	Ph
5	1	Me	OAc
6	1	HO	Me
9a	2	OAc	OAc
9b	2	Me	Me
10	2	HO	Me
11a	3	OAc	Me
11b	3	Me	OAc
16	1	H	H



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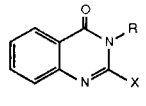
the structure of the 3-acetyl derivative was of interest. When the enol acetate **5** was cautiously treated with methanolic sodium methoxide a compound was obtained which analysed as a monoacetyl derivative of **1**. The infrared spectrum of this product contained a low intensity broad absorption due to a hydroxyl group and no peaks corresponding to a ketonic carbonyl group. The pmr spectrum was complex. The proton on C-3 appeared as an exchangeable doublet of doublets integrating for approximately half a proton and there were two methyl signals at δ 2.43 and δ 2.02. No peaks above δ 10.0 were observed but we have previously noted [3] that hydroxyl groups in enols of this type are often very broad and not easily observed. We conclude that in solution probably both enol and keto tautomers are present and that in the solid state the 3-acetyl derivative exists as the enol **6**. This prompted us to investigate the nature of the corresponding monoacetyl derivatives of **7** and **8**. When **7** was heated with acetic anhydride condensation was rapid and a two com-

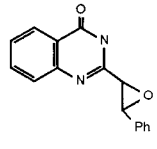
ponent solid was obtained from the reaction mixture. Purification by preparative thin layer chromatography gave an enol acetate **9a** or **9b** and a monoacetyl derivative. The infrared spectrum of this latter compound was similar to that of **6** and this, taken, in conjunction with its pmr spectral data indicated the enol **10**. It was not possible to deduce the stereochemistry of the enol acetate from its spectroscopic data.

We have previously reported [4,5] that the azepino analogue **8** is much less reactive than **1** and **7** and when **8** was heated under reflux with acetic anhydride no reaction occurred. However when the reaction was carried out in a sealed tube at 180° a very slow reaction took place and the enol acetate **11a** or **11b** was obtained. However due to the poor yield from this synthesis no attempt was made to investigate deacetylation of this product.

Both **3** and **6** reacted as carbonyl compounds, *e. g.* condensation between **3** and methyl vinyl ketone gave the spiroenone **12** whilst **6** formed a phenylhydrazone derivative **13**. It might therefore be reasonably expected that reduction of **3** would yield the desired intermediate **2** however when **3** was treated with sodium borohydride no alkanol was obtained. From the reaction mixture a two component solid crystallised which was subsequently purified by preparative thin layer chromatography. The less polar component was shown to be 2,3-dihydro-3-methylpyrrolo[2,1-*b*]quinazolin-9(1*H*)-one **14** on comparison with an authentic sample [4] whilst the more polar component was identified as the amine **15**. The formation of both these products can be rationalised by assuming that initially **2** is produced and then undergoes rapid dehydration to yield the 3-methylene derivative **16**. Reduction of **16** leads to **14** which is then further reduced [9] to the amine **15**. This hypothesis is supported by the results of attempted direct hydroxymethylation of **1** using an excess of formaldehyde and potassium hydroxide in ethanol. In addition to unreacted starting material a three component mixture was obtained from which the diol **17** crystallised. Purification of the residues gave both **16** and **18**. The formation of these products can be explained by again assuming that **2** is produced but is dehydrated to yield **16**. Nucleophilic attack by either hydroxide or ethoxide ion at the terminal carbon of the methylene group yields a resonance stabilised carbanion which then undergoes reaction with a further molecule of formaldehyde. A reaction mechanism of this type also accounts for the formation of **19** from the reaction between **1** and bis-(dimethylamino)methane in acetic anhydride [3]. In this case attack by acetate anion on **16** followed by reaction of the intermediate carbanion with a further molecule of bis-(dimethylamino)methane leads to the formation of **19**.



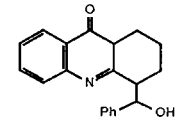
	R	X
21	CH_2CH_2OH	Me
23	CH_2CH_2OCOPh	CH=CHPh
22	CH_2CH_2OH	CH=CHPh
38	H	Me
39	CH_2CH_2C 2Me	Me
40	$CH_2CH_2CO_2Me$	CH=CHPh



	R
25	CH_2CH_2OCOPh
24	CH_2CH_2OH
41	$CH_2CH_2CO_2Me$
42	H

Oxygen Analogues.

We have also investigated the synthesis of oxygen analogues of **1**. Reaction of acetanthranil **20** with ethanolamine in dimethylformamide gave the alkanol **21** [10]. When **21** was heated with benzaldehyde two benzylidene derivatives **22** and **23** were produced both of which were converted into the epoxides **24** and **25** with 3-chloroperoxybenzoic acid. The mechanism for the formation of **23** probably involves some benzoylating agent produced in the autoxidation of the benzaldehyde. Treatment of **24** or **25** with methanolic sodium methoxide gave one major product with a molecular formula $C_{18}H_{16}N_2O_3$ as shown by analysis and mass spectrometry. Two possibilities exist for the structure of this compound *i. e.* **26** and **27**, however since alkanols of the type **26** undergo easy dehydration to



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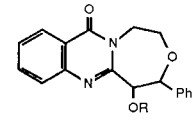
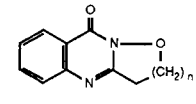


27 R = H
28 R = Ac

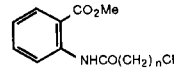


	n	X
29	1	CH
30	2	CH
33	3	CH
35	2	N

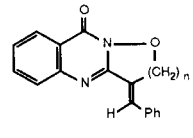
yield phenylmethylene derivatives we conclude that the oxazepino structure **27** is more probable. When **27** was treated with acetic anhydride only the acetate **28** was obtained.

Reisner [11] has described the synthesis of isoxazolo and [1,2] oxazino analogues of **1** but has not reported any oxazepino compounds. We have prepared both the above compounds and extended the method to prepare oxazepino analogues of **1**. Reaction of 3-chloropropionyl chloride and hydroxylamine followed by treatment of the intermediate with isatoic anhydride gave **29**. Compound **30** was obtained by the reaction of the ester **31** (derived from methyl anthranilate and 4-chlorobutyryl chloride) and hydroxylamine. When methyl anthranilate was treated with 5-chlorovaleryl chloride the ester **32** resulted and this could also be cyclised with hydroxylamine to afford the novel oxazepino analogue **33**. Pyrido analogues could also be prepared. Treatment of methyl 2-aminonicotinoate with 4-chlorobutyryl chloride gave the ester **34** which was not characterised but immediately treated with hydroxylamine to give a low yield of **35**. When **29** and **30** were heated with benzaldehyde the phenylmethylene derivatives **36** and **37** were produced. However **33** failed to condense with this reagent even after prolonged reflux.

The success of the method used to prepare **27** led us to attempt to prepare analogues of **1** using this route. Alkylation of 2-methylquinazolin-4-(3*H*)-one **38** with ethyl 3-bromopropionate gave, in low yield, the ester **39** which afforded a benzylidene derivative **40** when heated with benzaldehyde. A crystalline epoxide **41** resulted when **40** was oxidised with 3-chloroperoxybenzoic acid in dichloromethane. When **41** was treated with methanolic sodium methoxide no cyclisation took place and instead a retro Michael reaction occurred to yield **42**. The use of 2-carboethoxyethyl derivatives in the synthesis of heterocyclic thiols has been submitted for publication [12].



	n	X
31	3	CH
32	4	CH
34	3	N



36 n = 1
37 n = 2

EXPERIMENTAL

2,3-Dihydro-3-hydroxymethylenepyrrolo[2,1-*b*]quinazolin-9(1*H*)-one **3**.

This compound was prepared according to the method of Shakhidoyatov [7] and was obtained in 83% yield. An analytical sample was obtained by column chromatography as pale yellow needles mp 203-204° (reported my 205-206° [2]); ir (potassium bromide): 3700-3200, 1670, 1650, 1585 cm^{-1}.

2,3-Dihydro-3-(2-hydroxyethylidene)pyrrolo[2,1-*b*]quinazolin-9(1*H*)-one **6**.

A mixture of the enol acetate **5** [3] and methanolic sodium methoxide (prepared from sodium (5 mg) and methanol (110 ml)) was gently heated on a water bath. The solution soon turned black and the mixture was treated with a few drops of acetic acid. The solvents were removed *in vacuo* and the residue partitioned between water and dichloromethane. The dried organic phase was decolourised and concentrated to yield a yellow syrup which crystallised from ether as yellow needles (320 mg, 64%) mp 221-223°; ir (potassium bromide): 3225, 1670, 1640 cm^{-1}; pmr (hexadeuteriodimethylsulphoxide): 8.16-7.29 (4H, complex), 4.39 (~½H, dd, exchangeable), 4.05 (2H, t), 2.85 (1H, t), 2.48-2.27 (~3H, complex + s), 2.02 (~1H, s); ms: m/e 228 M^+.

Anal. Calcd. for $C_{13}H_{12}N_2O$: C, 68.4; H, 5.3; N, 12.3. Found: C, 68.1; H, 5.25; N, 12.1.

The phenylhydrazone **13** was obtained by reaction **6** with phenylhydrazine in ethanol containing acetic acid. Recrystallisation from ethanol gave pure **13** mp 185-186°; ir (potassium bromide): 3340, 1670, 1620 cm^{-1}; ms: m/e 318 M^+.

Anal. Calcd. for $C_{13}H_{18}N_4O$: C, 71.8; H, 5.7; N, 17.6. Found: C, 71.9; H, 5.7; N, 17.7.

Acetylation of 11*H*-6,7,8,9-Tetrahydropyrido[2,1-*b*]quinazolin-11-one **7**.

A mixture of **7** (1.5 g) and acetic anhydride (30 ml) was heated under reflux for 36 hours. The solvents were removed *in vacuo* and the residue passed through a small column of silica gel. A two component solid was obtained which was purified by preparative thin layer chromatography to yield 11*H*-6-(2-acetoxyethylidene)-6,7,8,9-tetrahydropyrido[2,1-*b*]-quinazolin-11-one **9a** or **9b** as pale yellow crystals (380 mg, 18%) mp 124-125° (ether); ir (potassium bromide): 1760, 1670, 1580 cm^{-1}; pmr (deuteriochloroform): 8.14 (1H, dd), 7.90-7.41 (3H, complex), 3.95 (2H, complex), 2.51 (2H, complex), 2.39 (3H, d, J = 2 Hz), 2.24 (3H, s), 1.89 (2H, complex); ms: m/e 284 (57%) M^+.

Anal. Calcd. for $C_{16}H_{16}N_2O_4$: C, 67.6; H, 5.6; N, 9.9. Found: C, 67.6; H, 5.7; N, 9.8.

A more polar band was removed from the plate to yield 11*H*-(2-hydroxyethylidene)-6,7,8,9-tetrahydropyrido[2,1-*b*]quinazolin-11-one **10** as a pale yellow powder (570 mg, 31%), mp 176-177° (ether); ir (potassium bromide): 1680 cm^{-1}; pmr (hexadeuteriodimethylsulphoxide): 8.04 (1H, d), 7.74-7.14 (3H, complex), 3.84 (2H, complex), 2.44 (2H, complex), 2.11 (3H, s), 1.95 (2H, complex); ms: m/e 242 (96%) M^+.

Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.4; H, 5.8; N, 11.6. Found: C, 69.3; H, 5.9; N, 11.5.

6-(2-Acetoxyethylidene)-7,8,9,10-tetrahydroazepino[2,1-*b*]quinazolin-12(6*H*)-one **11a** or **11b**.

A solution of **8** (1.5 g) in acetic anhydride (10 ml) was heated at 180° for 5 days (sealed tube). The reaction mixture was concentrated *in vacuo* and the residual solid purified by column chromatography on silica gel. Elution with light petroleum:ether (2:1) gave pure **11a** (or **11b**) (570 mg, 27%), as colourless crystals mp 116-117° (ether); ir (potassium bromide): 1760, 1670, 1590 cm^{-1}; pmr (deuteriochloroform): 8.30 (1H, dd), 4.30 (2H, complex), 2.35 (2H, complex), 2.25 (3H, s), 2.05 (3H, s), 1.76 (4H, complex); ms: m/e (85%) m^+.

Anal. Calcd. for $C_{17}H_{18}N_2O_3$: C, 68.5; H, 6.1; N, 9.4. Found: 68.3; H, 5.9; N, 9.4.

Reaction of **3** with Methyl Vinyl Ketone.

A mixture of **3** (1.0 g), methyl vinyl ketone (0.5 g) and triethylamine (0.2 g) was heated on a steam bath for 18 hours. The resulting black syrup was chromatographed to yield crude **12** which was further purified by preparative thin layer chromatography. The product was recrystallised from cyclohexane/ethyl acetate to yield colourless crystals of the pure spiro compound **12** mp 169-171°, (350 mg, 28%); ir (potassium bromide):

1690, 1685, 1670, 1620 cm^{-1}; pmr (hexadeuteriodimethylsulphoxide): 8.32-8.11 (1H, complex d), 7.91-7.42 (3H, complex), 7.06 (1H, d, J = 10 Hz), 6.06 (1H, d, J = 10 Hz), 3.93 (2H, complex), 2.71-2.16 (6H, complex).

Anal. Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.2; H, 5.3; N, 10.5. Found: C, 71.9; H, 5.3; N, 10.3.

Reduction of **3** with Sodium Borohydride.

Sodium borohydride (1.5 g) was added portionwise to a refluxing solution of **3** (3.0 g) in ethanol (150 ml). After about 4 hours a large quantity of **3** still remained and further borohydride (5 g) was added and the mixture heated under reflux overnight. The excess reagent was destroyed with acetic acid, and sodium bicarbonate solution added. The solvents were removed *in vacuo*, the residue extracted with dichloromethane and the extracts dried and concentrated *in vacuo*. The syrup was purified by passage through a short column of silica gel and then after concentration of the eluant further purified by preparative thin layer chromatography. Desorption of the least polar major band (Rf 0.68, triethylamine 1:ethyl acetate 9) gave 2,3-dihydro-3-methylpyrrolo[2,1-*b*]quinazolin-9-(1*H*)-one **14** (800 mg, 28%) identical in all respects (mp, mmp, ir and pmr) to an authentic sample [4].

Desorption of the more polar major band (Rf 0.48) gave 2,3,4a,4-tetrahydro-3-methylpyrrolo[2,1-*b*]quinazolin-9-(1*H*)-one **15** (500 mg, 18%), mp 181-186°; ir (potassium bromide): 3260, 1630 cm^{-1}; pmr (hexadeuteriodimethylsulphoxide): complex due to the fact that the product appears to be a mixture of isomers; ms: m/e 202 M^+.

Anal. Calcd. for $C_{12}H_{14}N_2O$: C, 71.3; H, 6.95; N, 13.85. Found: C, 70.8; H, 6.95; N, 13.85.

Reaction of **1** with Formaldehyde and Potassium Hydroxide.

A mixture of **1** (4.0 g), ethanol (180 ml), potassium hydroxide (11.0 g) and paraformaldehyde (26 g) was heated at 100° for 8 hours. The mixture was poured into water and neutralised with acetic acid. The solution was extracted three times with dichloromethane and the extracts dried and concentrated *in vacuo*. The resulting syrup rapidly partially crystallised and the solids were filtered and washed with a little ether. Recrystallisation from ethanol gave 2,3-dihydro-3,3-dihydroxymethylpyrrolo[2,1-*b*]-quinazolin-9(1*H*)-one **17** (0.5 g, 11%) mp 207.5-209° as colourless needles; ir (potassium bromide): 3700-3200, 1670, 1060 cm^{-1}; pmr (hexadeuteriodimethylsulphoxide): 8.13 (1H, complex d), 7.94-7.43 (3H, complex), 4.95 (2H, t, exchangeable), 3.99 (2H, t), 3.83-3.48 (4H, complex), 2.32 (2H, t); ms: m/e 246 M^+.

Anal. Calcd. for $C_{13}H_{14}N_2O_3$: C, 62.3; H, 5.8; N, 11.2. Found: C, 62.6; H, 5.8; N, 11.2.

The reaction residues were chromatographed on silica gel to yield a two component syrup (1.5 g) and unreacted **1** (400 mg). The two component syrup was purified by preparative thin layer chromatography. Desorption of the less polar band gave pure 2,3-dihydro-3-methylenepyrrolo[2,1-*b*]quinazolin-9(1*H*)-one **16** mp 144-145° (undepressed on admixture with an authentic sample and identical by ir and pmr [3]) as colourless needles (670 mg, 15%). Desorption of the more polar band gave colourless needles of 2,3-dihydro-3-ethoxymethyl-3-hydroxymethylpyrrolo[2,1-*b*]quinazolin-9(1*H*)-one **18** (700 mg, 13%), mp 82-84°; ir (potassium bromide): 3580, 3510, 1675, 1100, 1060 cm^{-1}; pmr (hexadeuteriodimethylsulphoxide): 8.16 (1H, d), 7.70-7.10 (3H, complex), 5.80-3.10 (9H, complex becoming 8H, complex on deuterium exchange), 2.38 (2H, t), 1.06 (3H, t); ms: m/e 274 M^+.

Anal. Calcd. for $C_{15}H_{18}N_2O_3$: C, 63.6; H, 6.4; N, 9.9. Found: C, 63.3; H, 6.7; N, 9.8.

3-(2-Hydroxyethyl)-2-methylquinazolin-4(3*H*)-one **21**.

A mixture of ethanolamine (8.0 g), acetanthranil (20 g) and dimethylformamide (200 ml) was heated under reflux for 3 hours. The solution was cooled and solvents removed *in vacuo* to yield a solid. The solid was broken up under ethyl acetate, filtered and washed with ethyl acetate to yield crude **21** (10.5 g). Recrystallisation from hot ethyl acetate gave fine needles of pure **21** (8.76 g, 35%), mp 161-163°, (reported [10] mp 156-157°); ir (potassium bromide): 3180, 3000, 2960, 2875, 1685, 1590, 1050 cm^{-1}; pmr (hexadeuteriodimethylsulphoxide): 8.00 (1H, d), 7.9-7.1 (3H, complex), 4.96 (1H, broad s, exchangeable), 4.3-3.5 (4H, complex becoming 4H, 2t on exchange), 2.64 (3H, s); ms: m/e 204 M^+.

Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.7; H, 5.9; N, 13.7. Found: C, 64.4; H, 5.9; N, 13.7.

Reaction Between **21** and Benzaldehyde.

A mixture of **21** (3.36 g) and benzaldehyde (10 ml) was heated under reflux for 3½ hours. The mixture was heated overnight to yield crude **22** (2.05 g). Recrystallisation from ethanol gave pure 3-(2-hydroxyethyl)-2-(2-phenylethenyl)quinazolin-4(3*H*)-one **23** as a pale-yellow solid (1.87 g, 39%), mp 180-181°; ir (potassium bromide): 3250, 3050, 2960, 1660, 1545, 1025 cm^{-1}; pmr (hexadeuteriodimethylsulphoxide): 8.2-7.4 (11H, complex), 5.06 (1H, t, J = 6 Hz, exchangeable), 4.36 (2H, t), 3.81 (2H, q becoming 2H, t on exchange); ms: m/e 292 (84%) m^+.

Anal. Calcd. for $C_{18}H_{16}N_2O_2$: C, 74.0; H, 5.5; N, 9.6. Found: C, 74.1; H, 5.7; N, 9.6.

The reaction residues were heated at reflux for a further 4 hours. The cooled mixture was treated with ether to yield crude **23** (1.50 g). Recrystallisation from hot ethanol gave pure 3-(2-benzoyloxyethyl)-2-(2-phenylethenyl)quinazolin-4(3*H*)-one **22** as pale yellow needles (1.13 g, 17%), mp 183-185°; ir (potassium bromide): 3045, 1710, 1665, 1550, 1280 cm^{-1}; pmr (deuteriochloroform): 8.14 (1H, d), 8.0-7.2 (15H, complex), 4.70 (4H, t); ms: m/e 396 M^+.

Anal. Calcd. for $C_{25}H_{20}N_2O_3$: C, 75.8; H, 5.1; N, 7.1. Found: C, 75.6; H, 5.1; N, 7.2.

3-(2-Benzoyloxyethyl)-2-(1,2-epoxy-2-phenylethyl)quinazolin-4(3*H*)-one **25**.

A solution of the alkene **23** (530 mg) in dichloromethane (100 ml) was stirred at room temperature and 3-chloroperoxybenzoic acid (400 mg) added. The mixture was stirred at room temperature for 2 days and then extracted with sodium bicarbonate solution. The dried organic phase was concentrated *in vacuo* and the residue recrystallised from methanol to yield pure **24** (290 mg, 53%), mp 143-144°; ir (potassium bromide): 1705, 1680, 1275, 1110 cm^{-1}; pmr (deuteriochloroform): 8.20 (1H, d), 8.0-7.1 (13H, complex), 4.61 (4H, s), 4.38 (1H, d, J = 2 Hz), 4.25 (1H, d, J = 2 Hz); ms: m/e 412 (18%) M^+.

Anal. Calcd. for $C_{25}H_{20}N_2O_4$: C, 72.8; H, 4.9; N, 6.8. Found: C, 72.5; H, 5.0; N, 6.9.

2-(1,2-Epoxy-2-phenylethyl)-3-(2-hydroxyethyl)quinazolin-4(3*H*)-one **24**.

A solution of the alkene **22** (1.05 g) in dichloromethane (150 ml) was stirred at room temperature and 3-chloroperoxybenzoic acid (780 mg) added. The mixture was stirred as above for 2 days and the product isolated as described for **24** to yield, after recrystallisation from methanol pure **25** (850 mg, 77%), mp 175-177°; ir (potassium bromide): 3405, 1680, 1060 cm^{-1}; pmr (hexadeuteriodimethylsulphoxide): 8.08 (1H, d), 7.9-7.1 (8H, complex), 5.0 (1H, t, J = 5 Hz, exchangeable), 4.58 (1H, d, J = 2 Hz), 4.34 (1H, d, J = 2 Hz), 3.9-4.3 (2H, complex), 3.71 (2H, t, J = 5 Hz); ms: m/e 308 (12%) m^+.

Anal. Calcd. for $C_{18}H_{16}N_2O_3$: C, 70.2; H, 5.2; N, 9.1. Found: C, 70.3; H, 5.4; N, 9.1.

11*H*-5-Hydroxy-1,2,4,5-tetrahydro-4-phenyl[1,4]oxazepino[5,4-*b*]quinazolin-11-one **27**.

(a) The epoxide **25** (740 mg) was added to a solution of sodium methoxide (from sodium (350 mg) in dry methanol (100 ml)) and the mixture allowed to stand overnight. The solvents were removed *in vacuo* to yield a crude solid (485 mg). Recrystallisation from dichloromethane/-ether gave pure **27** (350 mg, 63%), mp 151-153°; ir (potassium bromide): 3320, 1675, 1105 cm^{-1}; pmr (deuteriochloroform): 8.16 (1H, d), 7.9-7.0 (8H, complex), 5.6-4.8 (3H, complex becoming 2H, complex on deuterium exchange), 4.4-3.4 (4H, complex); ms: m/e 280 (12%) $(M\text{-}CO)^+$.

Anal. Calcd. for $C_{18}H_{16}N_2O_3$: C, 70.2; H, 5.2; N, 9.1. Found: C, 70.3; H, 5.4; N, 9.2.

(b) A solution of the epoxide **24** (700 mg) in methanolic sodium methoxide (prepared from sodium (250 mg) and dry methanol (100 ml)) was treated as in (a). The crude reaction product was recrystallised from

dichloromethane/ether to yield pure **27** (250 mg, 36%) identical in all respects (mp, mmp, ir and tlc) to the product obtained in (a).

11*H*-5-Acetoxy-1,2,4,5-tetrahydro-4-phenyl[1,4]oxazepino[5,4-*b*]quinazolin-11-one **28**.

A mixture of **27** (270 mg) and acetic anhydride (6 ml) was heated under reflux for 1 hour, cooled and the solvents removed *in vacuo*. The residue was partitioned between dichloromethane and sodium bicarbonate solution and the dried organic phase concentrated at reduced pressure to yield a colourless syrup which rapidly crystallised on the addition of ether. Recrystallisation from ethyl acetate/petrol gave pure **28** (260 mg, 85%) mp 163.5-164.5°; ir (potassium bromide): 1745, 1680, 1345, 1325 cm^{-1}; pmr (deuteriochloroform): 8.15 (1H, d), 7.85-7.05 (8H, complex), 5.2 (2H, complex), 4.4-3.4 (4H, complex), 2.04 (3H, s); ms: m/e 350 (0.2%) $m^{+\cdot}$.

Anal. Calcd. for $C_{20}H_{18}N_2O_4$: C, 68.6; H, 5.2; N, 8.0. Found: C, 68.7; H, 5.3; N, 8.2.

2,3-Dihydro-9*H*-isoxazolo[3,2-*b*]quinazolin-9-one **29**.

Hydroxylamine hydrochloride (34.8 g) was added to an ice-cold solution of sodium hydroxide (40 g) in water (600 ml). The solution was cooled to −5° (ice/salt bath) and 3-chloropropionyl chloride (58 g) was added dropwise with vigorous stirring at such a rate that the temperature of the solution remained at −5°. The solution was stirred for a further hour at −5° and a solution of sodium hydroxide (22 g) in water (50 ml) added and the solution stirred at 10-15° for 1 hour, and then at 60° for 1 hour. The solution was cooled again to 0°, chloroform (200 ml) and powdered isatoic anhydride (60 g) added. The resulting suspension was stirred at room temperature overnight, filtered and the organic phase separated. The aqueous phase was extracted (x 5) with chloroform and the total chloroform extracts dried, concentrated *in vacuo* to yield a white solid (12.0 g). Recrystallisation from ethyl acetate gave pure **29** (10.6 g, 15%), mp 157-158° (reported [11], mp 154-156°); ir (potassium bromide): 1680 cm^{-1}; pmr (deuteriochloroform): 8.09 (1H, d), 7.8-7.1 (3H, complex), 4.64 (2H, t), 3.56 (2H, t); ms: m/e 188 (100%) $m^{+\cdot}$.

Anal. Calcd. for $C_{10}H_8N_2O_2$: C, 63.8; H, 4.3; N, 14.9. Found: C, 64.0; H, 4.3; N, 15.0.

3,4-Dihydro[1,2]oxazino[3,2-*b*]quinazolin-10(2*H*)-one **30**.

A solution of methyl anthranilate (12.9) in dry pyridine (35 ml) was cooled to 0° and 4-chlorobutyryl chloride (12.0 g) added dropwise to the cooled solution. The mixture was stirred at room temperature overnight, the solvents removed *in vacuo* and the residue partitioned between ethyl acetate (250 ml) and water (50 ml). The dried extracts were concentrated *in vacuo* to yield a yellow syrup which contained (tlc) one very major product **32** and three very minor products. The crude **32** was dissolved in ethanol (25 ml) and added dropwise to an ice cold solution of hydroxylamine hydrochloride (11.9 g) and sodium hydroxide (10.2 g) in water (100 ml) at such a rate that the temperature was maintained between 0° and 5°. The mixture was stirred at room temperature overnight, then concentrated *in vacuo* to 100 ml and partitioned between water (100 ml) and chloroform (400 ml). The dried organic phase was concentrated *in vacuo* to yield crude **30** (5.87 g). Recrystallisation from hot ethyl acetate gave colourless needles of pure **30** (5.35 g, 31%), mp 154-155° (reported [11] mp 161-162°); ir (potassium bromide): 1695 cm^{-1}; pmr (deuteriochloroform): 8.30 (1H, dd), 7.9-7.2 (3H, complex), 4.43 (2H, t), 3.06 (2H, t), 2.37 (2H, complex); ms: m/e 202 (100%) $m^{+\cdot}$.

Anal. Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.3; H, 5.0; N, 13.9. Found: C, 65.7; H, 4.9; N, 13.9.

11*H*-2,3,4,5-Tetrahydro[1,2]oxazepino[3,2-*b*]quinazolin-11-one **33**.

A solution of methyl anthranilate (6.45 g) in dry pyridine (25 ml) was cooled to 0° and 5-chlorovaleryl chloride (6.62 g) added. The mixture was treated as previously described for **31** to yield crude **32** which solidified on standing. The crude ester was dissolved in ethanol (100 ml) and added dropwise to an ice cold solution of hydroxylamine hydrochloride (5.95 g) and sodium hydroxide (5.1 g) in water (50 ml) at such a rate that the temperature remained below 5°C. The mixture was treated as described for **30** to yield crude **33** (1.53 g, 17%), mp 145.5° (ethyl acetate); ir (potassium bromide): 1690, 1680 cm^{-1}; pmr (deuteriochloroform): 8.29 (1H, dt), 7.9-7.2 (3H, complex), 4.38 (2H, broad s), 3.14 (2H, broad s), 2.03 (4H, complex); ms: m/e 216 (100%) $m^{+\cdot}$.

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.7; H, 5.4; N, 13.0. Found: C, 66.7; H, 5.5; N, 13.0.

2*H*,10*H*-3,4-Dihydropyrido[2',3':4.5]pyrimido[3,2-*b*][1,2]oxazin-10-one **35**.

A solution of methyl 2-aminonicotinoate (13.68 g) in dry pyridine (50 ml) was cooled to 0° and 4-chlorobutyryl chloride (12.69 g) added dropwise. The mixture was treated exactly as described for **31** to yield crude **34**. This crude ester was chromatographed on silica gel to yield pure ester **34** (6.88 g) as a colourless oil. A portion of this purified ester (4.5 g) was dissolved in ethanol (50 ml) and the solution added to an ice cold solution of hydroxylamine hydrochloride (2.5 g) and sodium hydroxide (2.2 g) in water (25 ml). The addition was carried out at such a rate that the temperature remained below 5° and the mixture was stirred at 0° for one hour, and then at room temperature for 6 hours. The solvents were reduced to 20 ml *in vacuo* and the residue treated as described for **30** to yield a lemon yellow solid (1.2 g). Recrystallisation from hot ethyl acetate gave pure **35** as small colourless crystals (800 mg, 22%) mp 140-141°; ir (potassium bromide): 1700 cm^{-1}; pmr (deuteriochloroform): 8.76 (1H, dd), 8.41 (1H, dd), 7.21 (1H, dd), 4.42 (2H, t), 3.15 (2H, t), 2.36 (2H, complex); ms: m/e 203 (100%) $m^{+\cdot}$.

Anal. Calcd. for $C_{10}H_9N_3O_2$: C, 59.1; H, 4.4; N, 20.7. Found: C, 59.5; H, 4.6; N, 20.7.

2,3-Dihydro-3-phenylmethylene-9*H*-isoxazolo[3,2-*b*]quinazolin-9-one **36**.

Benzaldehyde (3 ml) and **29** (2 g) were heated at 180° for 5 minutes. The cooled mixture was treated with ether/ethanol to yield a pale brown solid (1.3 g). Recrystallisation from chloroform/ethyl acetate gave fine colourless needles of pure **36** (920 mg, 31%) mp 210-211°; ir (potassium bromide): 1670 cm^{-1}; pmr (deuteriochloroform): 8.34 (1H, complex), 7.9-7.2 (9H, complex), 5.60 (2H, d); ms: m/e 276 (100%) $m^{+\cdot}$.

Anal. Calcd. for $C_{17}H_{12}N_2O_2$: C, 73.9; H, 4.3; N, 10.1. Found: C, 74.0; H, 4.5; N, 10.3.

3,4-Dihydro-4-phenylmethylene[1,2]oxazino[3,2-*b*]quinazolin-10(2*H*)-one **37**.

Benzaldehyde (8 ml) and **30** (1.71 g) were heated at reflux for 10 minutes. The mixture was treated as described for **36** to yield crude **37** (495 mg). Recrystallisation from chloroform/ethyl acetate gave pure **37** as a pale yellow powder (360 mg, 15%), mp 220°; ir (potassium bromide): 1690 cm^{-1}; pmr (deuteriochloroform): 8.30 (1H, complex), 7.79 (1H, d, J = 3 Hz), 7.5-7.2 (8H, complex), 4.50 (2H, t), 3.28 (2H, dt); ms: m/e 290 (100%).

Anal. Calcd. for $C_{18}H_{14}N_2O_2$: C, 74.5; H, 4.8; N, 9.6. Found: C, 74.6; H, 4.9; N, 9.7.

3-(2-Carboethoxyethyl)-2-methylquinazolin-4(3*H*)-one **39**.

A mixture of **38** (5 g), ethyl 3-bromopropionate (5.94 g), potassium iodide (0.25 g), anhydrous potassium carbonate (4.74 g) and dry acetone (250 ml) was stirred at reflux overnight. The mixture was filtered, solids washed with acetone and the solvents removed *in vacuo*. The residue was extracted with ether/ethyl acetate and the concentrated extracts purified by passage through a small column of silica gel. Pure **39** was obtained as colourless plates (1.67 g, 21%), mp 102-103° (reported [13] mp 121°); ir (potassium bromide): 1725, 1670 cm^{-1}; pmr (deuteriochloroform): 8.09 (1H, complex d), 7.0-7.1 (3H, complex), 4.5-3.8 (4H, complex), 3.0-2.6 (5H, complex), 1.20 (3H, t); ms: m/e 260 (41%) $m^{+\cdot}$.

Anal. Calcd. for $C_{14}H_{16}N_2O_3$: C, 64.6; H, 6.2; N, 10.8. Found: C, 64.8; H, 6.3; N, 10.8.

3-(2-Carboethoxyethyl)-2-(2-phenylethenyl)quinazolin-4(3*H*)-one **40**.

Benzaldehyde (10 ml) and **39** (2 g) were heated under reflux for 2 hours. The cooled mixture was treated with ether to yield crude **40** (1.38 g) as a pale yellow solid. Recrystallisation from ethyl acetate/cyclohexane

gave pure **40** as fine pale yellow needles (1.21 g, 45%), mp 109-110°; ir (potassium bromide): 1720, 1670 cm^{-1}; pmr (deuteriochloroform): 8.10 (1H, d), 7.9-6.9 (10H, complex), 4.6-3.9 (4H, t + q), 2.79 (2H, t), 1.21 (3H, t); ms: m/e 348 (74%).

Anal. Calcd. for $C_{21}H_{20}N_2O_3$: C, 72.4; H, 5.7; N, 8.0. Found: C, 72.4; H, 5.9; N, 8.1.

3-(2-Carboethoxyethyl)-2-(1,2-epoxy-2-phenylethyl)quinazolin-4(3*H*)-one **41**.

A solution of 3-chloroperoxybenzoic acid (490 mg), **40** (710 mg) and dichloromethane (20 ml) was stirred at room temperature for 20 hours. The product was isolated as described for **24** as small white crystals (380 mg, 51%), mp 101°; ir (potassium bromide): 1720, 1680, 1360, 1220 cm^{-1}; pmr (deuteriochloroform): 8.16 (1H, d), 7.8-7.1 (8H, complex), 4.7-3.7 (6H, complex), 2.84 (2H, t), 1.13 (3H, t); ms: m/e 364 (5%) m^+.

Anal. Calcd. for $C_{21}H_{20}N_2O_4$: C, 69.2; H, 5.5; N, 7.7. Found: C, 69.2; H, 5.6; N, 7.7.

2-(1,2-Epoxy-2-phenylethyl)quinazolin-4(3*H*)-one **42**.

A solution of **41** (1.7 g) in dry tetrahydrofuran (100 ml) was stirred at room temperature and sodium hydride (230 mg, 50% dispersion in oil) added in small portions. No reaction took place, and a small quantity of damp tetrahydrofuran (5 ml) was cautiously added. The mixture was stirred at room temperature for 3 hours, absolute ethanol (5 ml) added dropwise and the solvents removed *in vacuo*. The residue was partitioned between water and dichloromethane/ethyl acetate (1:1) and the dried extracts concentrated *in vacuo* to yield a white solid. Recrystallisation from ethyl acetate gave pure **42** (1.03 g, 84%), mp 203-205°; ir (potassium bromide): 1675, 1615 cm^{-1}; pmr (deuteriochloroform): 12.24 (1H, broad s, exchangeable), 8.14 (1H, d), 7.8-7.1 (8H, complex), 4.10 (2H, d + d, J = 2 Hz); ms: m/e 264 m^+.

Anal. Calcd. for $C_{16}H_{12}N_2O_2$: C, 72.7; H, 4.5; N, 10.6. Found: C, 72.7; H, 4.5; N, 10.6.

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