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THE DEMONSTRATION OF NORMAL O → N CLAISEN REARRANGEMENT IN PURINES

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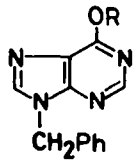
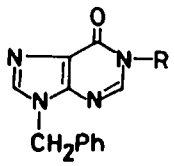
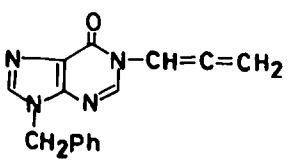
ABSTRACT : 6-Allyloxy-9-benzylpurine (2) and 9-benzyl-6-propargyloxy purine (5) undergo normal thermal O → N [3,3] rearrangement, either neat or in o-dichlorobenzene. The latter leads to the novel, 1-allenyl-9-benzyl-hypoxanthine (6). The related 4-allyloxy and 4-propargyloxy quinazolines (9, 12) also undergo smooth thermal O → N Claisen rearrangement. In the case of (12), the primary allenic product is further transformed into 3-propargylquinazolin-4-one (13) and the allene dimer (14).

Purines and related systems, having a number of ring nitrogens could undergo, normal or anionic or cationic or catalysed [3,3] rearrangement. The extensive studies by Leonard and co-workers have elegantly demonstrated the operation of anionic type Claisen rearrangement in guanines where the 6-O → 8-C ligand change occurs by two tandem [3,3] shifts[1]. A surprising aspect of this study was the finding that the normal [3,3] rearrangement of these systems was quite difficult. Thus, whilst 6-allyloxyguanine remained unchanged in refluxing DMF for 24 h and gave six products in refluxing triglyme for 4 h, its conjugate base underwent smooth tandem Cope rearrangement in diglyme during 5 h. Similar difficulties were experienced with 6- (2'-butenyloxy-3'-methyl) purine[1b]. We have found that 9-protected purines and the related quinazolines possessing either O-allyl or O-propargyl ligands undergo normal [3,3] rearrangement either neat or in refluxing o-dichlorobenzene[2]. This finding is noteworthy since it establishes the operation of normal [3,3] rearrangement in purines and related systems and identifies these amongst the handful of compounds that undergo O → N Claisen rearrangement[3].

9-Benzyl-6-chloropurine (1) on treatment with $H_2C{=}CH{-}CH_2ONa$ in allyl alcohol at reflux for 15 h gave 6-allyloxy-9-benzylpurine (2, 71%). Compound (2) when sealed under nitrogen and held neat at 180-190°C for 6 h gave the Claisen rearrangement product 1-allyl-9-benzylhypoxanthine (3, 30%). The structural assignment for (3) is supported by spectral and analytical data and by comparison with an authentic sample prepared in 56% yield by alkylation of the conjugate base of 9-benzylhypoxanthine (4)-generated with 1.2 eq of NaOMe in dry MeOH- with 1.2 eq of allylbromide[4]. Compound (1) on reflux in propargyl alcohol containing 1.1 eq of $HC{\equiv}CH{-}CH_2ONa$ for 2 h gave 9-benzyl-6-propargyloxypurine (5, 80%) which in o-dichlorobenzene at 145°C during 2 h underwent smooth Claisen rearrangement giving rise to the novel allenic compound (6) (50%). The presence of the significantly downfield (202.2 ppm) peak typical for allenic sp carbon and other spectral data support the structural assignment for (6). The Claisen rearrangement offers the best route to the reactive molecule(6), since attempted preparation of (6) by NaOMe catalysed isomerization of 9-benzyl-1-propargylhypoxanthine (7) gave mixtures. Compound (7), in turn, was prepared in 86% yield from propargylbromide and (4), as described for (3).



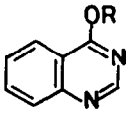


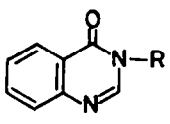


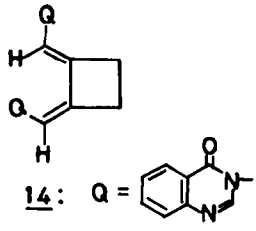
2: R = $-CH_2-CH=CH_2$ **3**: R = $-CH_2-CH=CH_2$ **6**

5: R = $-CH_2-C\equiv C-H$ **7**: R = $-CH_2-C\equiv C-H$

The purine ring system is considered as a composite of the electron rich imidazole and electron deficient pyrimidine[5]. We report that quinazolines, consisting of the pyrimidine part, undergo facile O → N Claisen rearrangement. 4-Chloroquinazoline (**8**) on treatment with 1.2 eq. of $H_2C=CH-CH_2ONa$ in allyl alcohol gave 4-allyloxyquinazoline (**9**; 89%), which, when held neat under nitrogen at 190-200°C for 24 h, underwent smooth Claisen rearrangement to 3-allylquinazolin-4-one (**10**; 75%). An authentic sample of (**10**) was prepared by direct alkylation of the sodium salt of quinazolin-4-one (**11**) in 85% yield. 4-Propargyloxyquinazoline (**12**)-prepared in 60% yield from (**8**)-in o-dichlorobenzene at 170-180°C for 12 h, gave 3-propargylquinazolin-4-one (**13**, 22%) and the allene dimer **14** (13%), mp 309°C[6]. Thus, whereas in the Claisen rearrangement of the purine (**5**), the allenic product (**6**) was quite stable, that with the quinazoline (**12**), the resulting allene partly dimerized to (**14**) and partly underwent isomerization to (**13**)[7]. An authentic sample of (**13**) was prepared by alkylation of the conjugate base of (**11**).



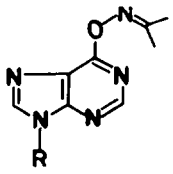


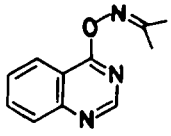


9: R = $-CH_2-CH=CH_2$ **10**: R = $-CH_2-CH=CH_2$ **14**: Q =

12: R = $-CH_2-C\equiv C-H$ **13**: R = $-CH_2-C\equiv C-H$

We have also examined the Claisen rearrangements in these systems involving the change, X-N → C-N (X=O or NH)[8]. The oxime ethers (**15**) and (**18**) were prepared in 62% and 90% yields respectively, by reaction of acetone oxime conjugate base with (**1**) and (**8**). 6-Chloro-9-tetrahydropyranylpurine yielded the oxime ether **16** (76%) in a similar manner. Thermolysis of either (**15**) or (**16**) in o-dichlorobenzene or neat gave, as the only isolable products, 9-benzylhypoxanthine (**4**) and 9-tetrahydropyranylhypoxanthine, most likely arising from Beckmann rearrangement involving the purinyloxy unit as the leaving group[9] and in preference to prototropic shift followed by Claisen rearrangement.

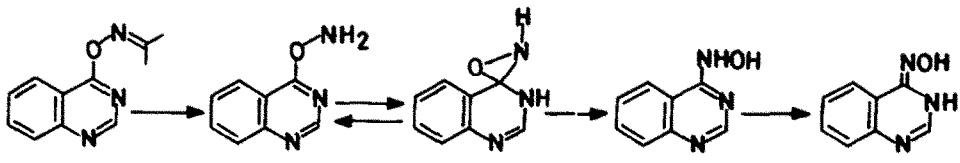




15: R = $-CH_2Ph$ **18**

16: R = -THP

Surprisingly, the quinazoline oxime ether (**18**) on neat thermolysis yielded 20% of 4-oximino quinazoline (**19**). The (**18**) → (**19**) change can best be rationalised on the basis of hydrolysis, oxazirane formation and C-O bond rupture[9].



18 19

Finally, the known 4-isopropylidenehydrazinoquinazoline[10] on attempted thermal polyhetero-Claisen rearrangement underwent fragmentation leading to the eventual isolation of quinazolin-4-one (11). The Claisen rearrangement should provide superior strategies towards the preparation of diverse 1-substituted purines. This aspect is being examined currently.

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Experimental[11]

I. The reaction of 9-benzyl-6-chloropurine (1) with sodium allyloxide : Preparation of 6-allyloxy-9-benzylpurine (2) :

Under stirring, 9-benzyl-6-chloropurine (1.5g, 6.1 mmol)[12] was added to a solution of sodium allyloxide in allyl alcohol - prepared from sodium (0.14g, 6.1 mmol) and allyl alcohol (~ 20 ml) - the mixture refluxed for 1.5 h, filtered, the filtrate evaporated, the residue triturated with hot benzene (~ 50 ml), decanted and evaporated to give 1.15g (70%) of 6-allyloxy-9-benzylpurine (2) as colourless needles, mp 65°C (Found : C, 67.87; H, 5.43; Calc. for $C_{15}H_{14}N_4O$: C, 67.67; H, 5.26%); IR : ν_{max}(KBr) cm^{-1} 3080, 3020, 1600, 1580, 1050; NMR : δ ($CDCl_3$) 5.1 (m, 2H), 5.38 (m, 4H), 6.18 (m, 1H), 7.28 (s, 5H), 7.8 (s, 1H), 8.5 (s, 1H).

II. Thermal rearrangement of 6-allyloxy-9-benzylpurine (2) : Isolation of [3,3] product, 1-allyl-9-benzylhypoxanthine (3) :

Under nitrogen, 6-allyloxy-9-benzylpurine (2, 1.0g, 3.76 mmol) was sealed and held at 180-190°C for 6 h, cooled, extracted with CH_2Cl_2, the organic extract passed through a short bed of silica gel topped with activated charcoal, solvents evaporated and the residue on crystallization from benzene gave (3) as colourless prisms, mp. 114-116°C, yield 0.29 g (29%) (Found : C, 67.84; H, 4.88; Calc. for $C_{15}H_{14}N_4O$: C, 67.67; H, 5.26%); IR : ν_{max} (KBr) cm^{-1} 3100, 3040, 1685, 1580, 1545, 1515; NMR : δ ($CDCl_3$) 4.66 (dd, 2H), 5.2 (m, 4H), 5.9 (m, 1H), 7.2 (s, 5H), 7.6 (s, 1H), 7.9 (s, 1H).

III. The reaction of 9-benzylhypoxanthine (4) with allylbromide : Preparation of 1-allyl-9-benzylhypoxanthine (3) :

Allylbromide (0.121g, 1.2 mmol) was added to a stirred solution of the sodium salt of 9-benzylhypoxanthine (4)[13] in MeOH -prepared from Na (0.027g, 1.2 mmol) in dry methanol (~15 ml) and (4) (0.226g, 1 mmol)- the reaction mixture refluxed for 2 h, cooled, solvents evaporated and the residue chromatographed on silica gel. Elution with PhH:EtOAc::1:1 gave 0.15 g (56%) of 1-allyl-9-benzylhypoxanthine (3) as colourless prisms, mp. 116°C, which was identical to sample obtained from Experiment II.

IV. The reaction of 9-benzyl-6-chloropurine(1) with sodium propargyloxide : Preparation of 9-benzyl-6-propargyloxypurine (5) :

9-Benzyl-6-chloropurine (1, 0.7g, 2.9 mmol) was added to a stirred solution of sodium propargyloxide in propargyl alcohol- prepared from sodium (0.07g, 3.19 mmol) and propargyl alcohol (~ 10 ml)- the mixture refluxed for 2 h, cooled, solvents evaporated, the residue mixed with water (~ 100 ml), filtered, dried and chromatographed. Elution with PhH:EtOAc::3:7 gave 0.5 g (80%) of 9-benzyl-6-propargyloxypurine (5) as colourless needles, mp. 117-118°C (Found : C, 68.05; H, 4.31; N, 21.73; Calc. for $C_{15}H_{12}N_4O$: C, 68.1; H, 4.5; N, 21.2%); IR : ν_{max} (KBr) cm^{-1} 3320, 3100, 1610, 1585; ^{1}H-NMR : δ ($CDCl_3$) 2.5 (t, 1H), 5.25 (d, 2H), 5.43 (s, 2H), 7.3 (s, 5H), 7.92 (s, 1H), 8.6 (s, 1H); ^{13}C-NMR (67.8 MHz) : δ ($CDCl_3$) 159.3, 153.3, 150.3, 143.9, 140.8, 135.1, 130.1, 129.6, 128.8, 127.8, 126.5, 73.2 (CH_2-C ≡CH), 54.0 (-O$\underline{C}H_2$), 47.4 ($\underline{C}H_2$Ph);m/z: 264 (M^+), 209 (M^+-(-OCH_2-C≡CH)), 173 (M^+ - ($PhCH_2$)), 91 ($PhCH_2^+$).

V. Thermal rearrangement of 9-benzyl-6-propargyloxypurine (5) : Isolation of allene (6) :

A stirred solution of (5) (0.236g, 0.9 mmol) in o-dichlorobenzene (~ 10 ml) was held at 145°C for 2 h, cooled, solvents evaporated, the residue subjected to preparative TLC using PhH:EtOAc:: 7:3 as developer and the resulting fraction on crystallization from benzene gave colourless prisms of (6), mp 161°C, yield 0.06g (50%); IR : ν_{max} (KBr) cm^{-1} 3090, 3060, 1950, 1690, 1570; ^{1}H -NMR : δ ($CDCl_3$) 5.3 (s, 2H), 5.6 (d, 2H), 7.24 (s, 5H), 7.62 (s, 1H), 7.75 (br, 1H), 8.14 (s, 1H); ^{13}C-NMR : δ ($CDCl_3$)

202.2 (-CH=C=CH$_2$), 154.8 (C=O), 88.6 (CH=C=CH$_2$), 47.5 (CH$_2$Ph); m/z : 264 (M^+). The preparative tlc also afforded 0.11g of unchanged (5).

VI. The reaction of 9-benzylhypoxanthine (4) with propargyl bromide : Preparation of 9-benzyl-1-propargylhypoxanthine (7) :

Propargyl bromide (0.357g, 3 mmol) was added to a stirred solution of the sodium salt of (4) in MeOH-prepared from Na (0.052g, 2.25 mmol) in dry methanol (~ 15 ml) and (4) (0.339g, 1.5 mmol)-the mixture left stirred at rt. overnight, solvents evaporated and the residue chromatographed on silica gel. Elution with EtOAc gave 0.34g (86%) of 9-benzyl-1-propargyl hypoxanthine (7) as colourless needles, mp 142°C; IR : ν_{max} (KBr) cm^{-1} 3230, 1685; ^{1}H-NMR : δ($CDCl_3$) 2.53 (t, 1H), 4.82 (d, 2H), 5.32 (s, 2H), 7.27 (s, 5H), 7.77 (s, 1H), 8.27 (s, 1H); m/z : 264 (M^+).

VII. The reaction of 4-chloroquinazoline (8) with sodium allyloxide : Preparation of 4-allyloxyquinazoline (9) :

4-Chloroquinazoline (8) (1.2g, 7.2 mmol)[14] was added to a solution of sodium allyloxide in allyl alcohol-prepared from Na (0.2g, 8.7 mmol) and allyl alcohol (~ 10 ml)-the mixture refluxed for 3 h, cooled, solvents evaporated, the residue triturated with benzene, decanted, evaporated and the resulting viscous oil distilled to give 1.2 g (89%) of 4-allyloxyquinazoline (9) bp. 130°/0.2 torr; (Found: C, 71.0; H, 5.21; N, 15.4; Calc. for $C_{11}H_{10}N_2O$: C, 70.96; H, 5.37; N, 15.05%); IR : ν_{max} (neat) cm^{-1} 3070, 3040, 1620, 1570; ^{1}H-NMR : δ($CDCl_3$) 5.0 (m, 2H), 5.2 (m, 2H), 6.1 (m, 1H), 7.25-8.5 (m, 4H), 8.66 (s, 1H).

VIII. Thermal rearrangement of 4-allyloxyquinazoline (9) : Isolation of [3,3] product 3-allylquinazolin-4-one (10) :

Under nitrogen, 4-allyloxyquinazoline (9) (1g, 5.37 mmol) was sealed, held at 190-200°C for 24 h, cooled, cautiously opened, extracted with CH_2Cl_2, evaporated and chromatographed on silica gel. Elution with PhH:EtOAc::4:1 gave 0.75g (75%) of 3-allylquinazolin-4-one as white crystals, mp. 65°C (Found: C, 71.06; H, 5.33; Calc. for $C_{11}H_{10}N_2O$: C, 70.96; H, 5.37%) ; IR : ν_{max} (KBr) cm^{-1} 1675, 1615, 1570; ^{1}H-NMR : δ($CDCl_3$) 4.55 (m, 2H), 5.18 (m, 2H), 5.88 (m, 1H), 7.2-7.9 (m, 4H), 8.1 (m, 1H).

IX. The reaction of 4-chloroquinazoline (8) with sodium propargyloxide : Preparation of 4-propargyloxyquinazoline (12) :

4-Chloroquinazoline (8, 3.29g, 20 mmol) was added to a stirred solution of sodium propargyloxide in propargyl alcohol-prepared from sodium (0.55g, 24 mmol) and propargyl alcohol (~20 ml)-the mixture refluxed for 2 h, solvents evaporated, the residue mixed with cold water (~ 100 ml), filtered, washed with water, dried and chromatographed. Elution with benzene gave 2.1g (57%) of 4-propargyloxyquinazoline (12) as colourless needles, mp. 127°C (Found: C, 72.23 ; H, 4.58; N, 15.08% ; Calc for $C_{11}H_8N_2O$: C, 71.73; H, 4.34; N, 15.21%); IR : ν_{max} (KBr) cm^{-1} 3180, 1600, 1565; NMR : δ($CDCl_3$) 2.45 (t, 1H), 5.17 (d, 2H), 7.5-8.3 (m, 4H), 8.7 (s, 1H).

X. Thermal rearrangement of 4-propargyloxyquinazoline (12) : Isolation of 3-propargylquinazoline-4-one (13) and the allene dimer (14) :

A stirred solution of (12) (0.5g, 2.7 mmol) in o-dichlorobenzene (~ 10 ml) was held at 180°C for 12 h, cooled, solvents evaporated and the residue chromatographed on silica gel. Elution gave with PhH: EtOAc::85:15, 0.09g (18%) of unchanged (12), mp 127°C and with PhH:EtOAc::8:2, 0.11g (22%) of 3-propargylquinazolin-4-one, (13) as colourless needles mp 116°C (lit.[15] mp 116-118°C); IR : ν_{max} (KBr) cm^{-1} 3230, 1665, 1600; ^{1}H-NMR : δ ($CDCl_3$) 2.53 (t, 1H), 4.85 (d, 2H), 7.5-8.5 (m, 5H); m/z : 184 (M^+), 156 (M^+-CO), 129 (M^+-(CO+HCN)), 102 (M^+-(CO+2HCN)). Further elution with PhH:EtOAc::4:6 gave the allene dimer (14) mp. 309°C, yield 0.13g (13%); (Found C, 71.27; H, 4.15; N, 15.64; Calc. for $C_{22}H_{16}N_4O_2$: C, 71.73; H, 4.34; N, 15.21; ^{1}H-NMR : δ ($CDCl_3$) 2.46 (s, 2H), 2.68 (s, 2H), 7.3-8.4 (m, 11H), 10.4 (s, 1H); m/z : 368 (M^+).

XI. The reaction of quinazoline-4-one (11) with propargyl bromide : Preparation of 3-propargylquinazolin-4-one (13) :

Propargyl bromide (1.19g, 10 mmol) was added to a stirred solution of the sodium salt of (11) in MeOH-prepared from Na (0.172g, 7.5 mmol) in dry methanol (~ 30 ml) and (11) (0.73g, 5 mmol)-the mixture left stirred at rt. overnight, solvents evaporated and the residue chromatographed on silica gel. Elution with PhH:EtOAc::8:2 gave 0.73g (91%) of (13), mp 117°C. This sample was identical to that obtained from Experiment X.

XII. The reaction of 4-chloroquinazoline (8) with acetoxime : Preparation of quinazoline oxime ether (18) :

4-Chloroquinazoline (2g, 12.1 mmol)[14] was added in portions to a stirred solution of the sodium salt of acetoxime-prepared from sat. aqueous NaOH (0.6g, 15 mmol) and acetoxime (1g, 13.7 mmol)-the mixture left stirred at rt. for 3 h, extracted with ether, dried ($MgSO_4$) and solvents evaporated to give 2.2g (90%) of (18) as a viscous liquid; IR ν_{max} (neat) cm^{-1} 1620, 1570; ^{1}H-NMR : δ ($CDCl_3$) 1.95 (s, 6H), 7.1-8.0 (m, 4H), 8.66 (s, 1H).

XIII. Thermolysis of quinazoline oxime ether (18) : Isolation of rearranged product (19) :

Under nitrogen, the oxime ether (18) (1g, 4 mmol) was held at 160°C for 6 h, cooled, extracted with CH_2Cl_2, solvents evaporated and the residue on preparative tlc using EtOAc as developer gave 0.16g (20%) of (19), mp. 205°C; IR : ν_{max} (KBr) cm^{-1} 3340 (br), 1685, 1585, 1560, 1520; ^{1}H-NMR: δ ($CDCl_3$) 7.48 (m, 1H), 7.63 (t, 1H), 7.76 (m, 2H), 8.1 (m, 2H), 8.32 (s, 1H); m/z : 161 (M^+).

XIV. The reaction of 9-benzyl-6-chloropurine (1) with acetoxime : Preparation of purine oxime ether (15) :

9-Benzyl-6-chloropurine (1, 0.5g, 2.05 mmol) was added in portions to a stirred solution of acetoxime sodium salt prepared from aq. NaOH (0.122g, 3.3 mmol) and acetoxime (0.224g, 3.1 mmol)- the mixture left stirred at rt. overnight, filtered, washed with water, dried and crystallised from ethyl acetate to give 0.345g (62%) of (15) as shining needles, mp. 170°C (Found: C, 64.03; H, 5.23; N, 24.64; Calc. for $C_{15}H_{15}N_5O$: C, 64.05; H, 5.34; N, 24.91%); IR : ν_{max} (KBr) cm^{-1} 1590, 1570, 1060; ^{1}H-NMR: δ ($CDCl_3$) 2.1, 2.2 (s, s, 3H, 3H), 5.4 (s, 2H), 7.3 (s, 5H), 7.9 (s, 1H), 8.7 (s, 1H).

XV. The reaction of 6-chloro-9-tetrahydropyranylpurine with acetoxime : Preparation of purine oxime ether (16) :

6-Chloro-9-tetrahydropyranylpurine (2.0g, 8.35 mmol) was transformed, by procedure described in Experiment XIV, in 76% yield to the oxime ether (16); mp. 135°C (Found: C, 56.28; H, 5.98; Calc. for $C_{13}H_{17}N_5O_2$: C, 56.72; H, 6.18%); IR: ν_{max} (KBr) cm^{-1} 2950, 2810, 1590, 1570, 1540, 1050; ^{1}H-NMR : δ ($CDCl_3$) 1.9 (m, 6H), 2.1, 2.2 (s, s, 3H, 3H), 3.9 (m, 2H), 5.6 (m, 1H), 8.0 (s, 1H), 8.5 (s, 1H).

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b. N.J. Leonard and C.R. Frihart, J. Am. Chem. Soc., 96, 5894 (1974);
c. B.N. Holmes and N.J. Leonard, J. Org. Chem., 41, 568 (1976).

2. Surprisingly, excepting for a single report in 1935 (E. Bergmann and H. Heimold, J. Chem. Soc., 1365 (1935)), which has been noted but not commented upon (ref.1) and those cited above, there has been no study of Claisen rearrangement of purines and related quinazolines. In the light of observations of Leonard and co-workers and ourselves, we feel that the pioneering work of Bergmann and Heimold merits re-examination. The first of the Claisen rearrangements reported in the paper, relates to the thermolysis of 2, 6-diallyloxy-7-methypurine at 150°C for 2 h. The yields are unstated, allylamine smell was observed (?) and the only proof for the structure is the inertness of the product towards hydrogenolysis, which merely shows that the initial O-C bond is not present. We have found that 6-allyloxy-7-benzylpurine, unlike the 9-benzyl analog does not undergo rearrangement at 200°C for 6 h. The second, that reports the formation of the Claisen product, again in unstated yields, from 2, 6-dichloro-7-methylpurine, in one flask, by treatment with vast excess of MeCH=CH-CH(OH)Et containing sodium at 165°C for 4 h, followed by dilution with water, extraction with ether, evaporation and distillation, appears improbable, particularly in view of the instability of the product, if formed, to alcohol, alkoxides and alkali.

3. In general, the O → N shift is less preferred over O → C. A good illustration of this is the exclusive thermal rearrangement of O-allylhexanolactim to 3-allylhexanolactam, although the pathway requires the prior migration of N=C→C=C (D.St.Black and A.M. Wade, J. Chem. Soc., Chem. Comm., 871 (1970)). It is thought that the oxygen lone pair contribution that would reduce the C=N π bond order and enhance the nitrogen nucleophilicity would promote the O → N (3,3) shift (J.K. Elwood and J.W. Gates Jr., J. Org. Chem., 32, 2956 (1957)). This concept is useful in the understanding of the behaviour of systems capable of undergoing O → N (3,3), which have thus far been studied : Whilst 2-allyloxypyrimidine and 3-allyloxypyrazole gave none of the possible O → N (3,3) products, 2-allyloxybenzothiazole and benzoxazole and 5-allyloxy-1-phenyltetrazole underwent O → N Claisen rearrangement (J.K. Elwood and J.W. Gates Jr., J. Org. Chem., 32, 2956 (1957)). 2-Allyloxypyridine yielded equal amounts of O→ C and O → N Claisen products; 2-Substituted-4-allyloxypyrimidines largely afforded O → C compound and 4-allyloxy-N-methyluracil exclusively the O → N (3,3) rearranged compound (F.J. Dinan and H. Tieckelmann, J. Org. Chem., 29, 892 (1964) ; H.J. Minnemeyer, P.B. Clarke and H. Tieckelmann, J. Org. Chem., 406 (1966)). Exclusive O → N rearrangement of 2-allyloxypyridine can be brought about by use of either H_2PtCl_6 or $Pt(PPh_3)4$ as catalysts at relatively low temperatures (H.F. Stewart and R.P. Seibert, J. Org. Chem., 33, 4560 (1968); G. Balavoine and F. Guibe, Tetrahedron Lett., 3949 (1979)). The pathways involved in these reactions are not certain (R.P. Lutz, Chem. Rev., 84, 205 (1984)).

4. The overall yield of (3) by (3,3) shift and by direct alkylation of (4) are comparable since the latter is prepared by dilute HCl hydrolysis of (1).

5. J.H. Lister, "Fused Pyrimidines", Part II, Ed. D.J. Brown, Wiley-Interscience, 1971, p.7.

6. The structural assignment for 14 is supported by NMR and MS data. The presence of a non-exchangeable, single proton peak at δ10.4 and singlets at δ2.68 and δ2.64, for 2 protons each, clearly favour the proposed "in-out" orientation of the quinazolin-4-one unit. In such structures, it is known that the "in" proton is heavily de-shielded and the two sets of geminal protons appear separately with little vicinal coupling. Although dimerization of allenes with nitrogen functionalities directly connected to the propadiene is not reported so far, mono-substituted allenes are known to yield 1,2-alkylidene/arylidene cyclobutanes in which the "out-out" dimer is least favoured. The preference for the "in-in" orientation can be altered to the "in-out" by large substituents (H.F. Schuster and G.M. Coppola, "Allenes in Organic Synthesis", Wiley-Interscience, 1984; D.J. Pasto, Tetrahedron, 40, 2989 (1984); J.E. Baldwin and R.H. Fleming, Fortschr.

Chem. Forsch., 15, 281 (1970); O.J. Muscio and T.L. Jacobs, Tetrahedron Lett., 2867 (1969); T.L. Jacobs and O.J. Muscio, Tetrahedron Lett., 4829 (1970); J.J. Gajewski and C.N. Shih, J. Am. Chem. Soc., 91, 5900 (1969); J. Org. Chem., 37, 64 (1972)).

We thank the referee for very pertinent suggestions relating to the structure of 14.

7. Interestingly, the O → N (3,3) of 2-allyloxyquinoline is quite difficult. Even at 250°C the transformation is poor; at 300°C mixtures result (Y. Makisumi, Tetrahedron Lett., 2833 (1964)).

8. Enamines arising from prototropic shift of O-vinyl oxime ether types can undergo O-N → C-C (3,3) shift (T. Sheradsky, Tetrahedron Lett., 25 (1970)). The N-N → C-C (3,3) shift is a key requirement in the Fisher indole synthesis.

9. We are grateful to the referee for suggesting the pathway, which, we feel, is very reasonable.

10. S. Asano and H. Asai, Japan Pat., 3376 (59); Chem. Abstr., 54, 14277 (1960).

11. MPs are not corrected. IR spectra were recorded in a PE 580 instrument as KBr discs. NMR spectra were obtained on a 10-15% solution in $CDCl_3$ or $DMSO(d_6)$ on a F T R-600 instrument, unless otherwise stated. The chemical shifts are recorded in ppm with TMS at 0.00 as internal standard. Mass spectra were obtained on a Jeol instrument. Silica gel (Acme) was used for TLC and column chromatography (100-200 mesh). Reactions were monitored wherever possible by TLC. The organic extracts were invariably dried over anhyd. $MgSO_4$ and solvents evaporated in vacuo.

12. J.A. Montgomery and C. Temple, J. Am. Chem. Soc., 83, 630 (1961).

13. E. Shaw, J. Org. Chem., 30, 3371 (1965).

14. W.L.F. Armarego, J. Appl. Chem., 11, 70 (1961).

15. C. Bogentoft, O. Ericsson, P. Stenberg and B. Danielsson, Tetrahedron Lett., 4745 (1969).