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Triazolopyridines. 18.[1] Nucleophilic Substitution Reactions on Triazolopyridines; A New Route to 2,2'-Bipyridines

Gurnos Jones,[a]* Mark A. Pitman,[a] Edward Lunt,[b] David J. Lythgoe,[b] Belén Abarca,[c]* Rafael Ballesteros,[c] and Mostafá Elmasnaouy[c]

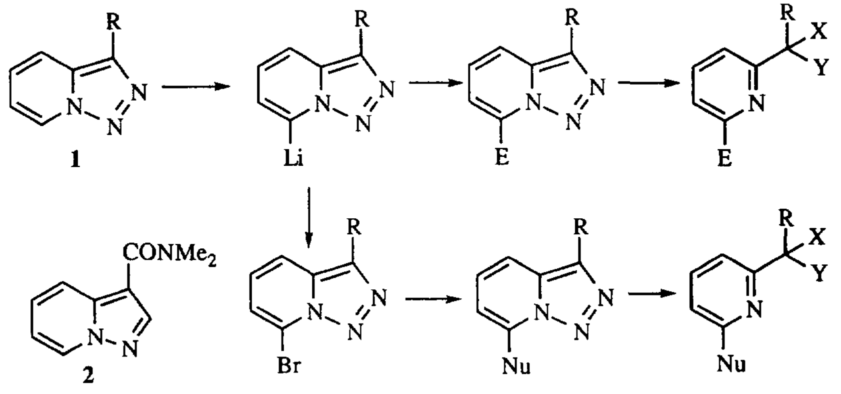
[a] Chemistry Department, Keele University, Staffordshire, ST5 5BG, U K.

[b] Rhône-Poulenc Rorer Ltd., Dagenham Research Centre, Rainham Road South, Dagenham, Essex, RM10 7XS, UK.

[c] Departamento de Quimica Orgánica, Facultad de Farmacia, Universidad de Valencia, Avda. Vicente Andrés Estellés s/n, 46100 Burjassot (Valencia), Spain.

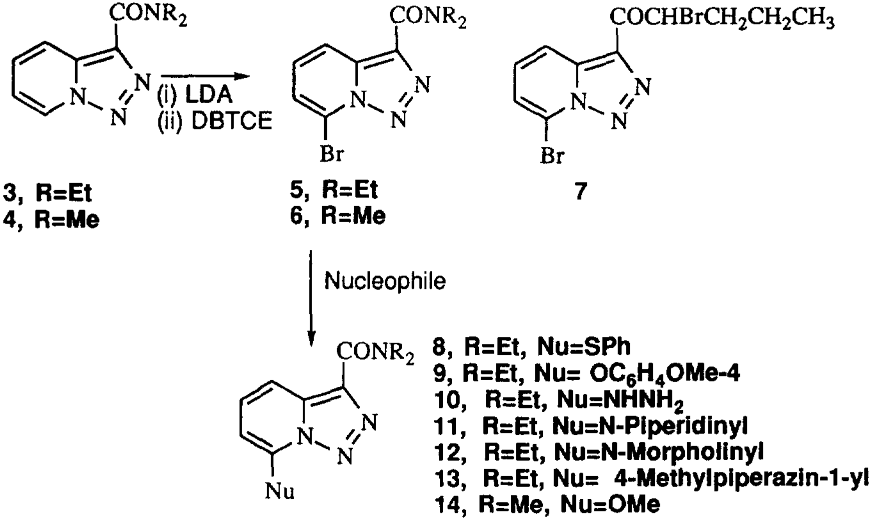
Abstract; The synthesis of some 5-, 6-, and 7-halogenotriazolopyridines is described. and their reactions with nucleophiles. The formation of 7,7'-bitriazolopyridines provides a new synthesis of 2,2'-bipyridines.

We have reported[2] that triazolopyridines of general type **1** undergo ring opening under a variety of conditions, with loss of dinitrogen, to give 2-substituted pyridines. Since 7-substituted triazolopyridines are readily available by regioselective lithiation of the parent, or of 3-substituted triazolopyridines, and subsequent reaction with electrophiles,[3] a synthesis of 2,6-disubstituted pyridines is thereby achieved. We have also found[4] that a bromine atom at position 7 is readily replaced by nucleophiles, thus widening the scope of the synthesis further. The complete range of possibilities is summarized in Scheme 1. The discovery that pyrazolopyridines, particularly the amide **2**, showed valuable properties in inhibiting disease progression in arthritic disorders[5], led us to attempt the synthesis of a range of similar triazolopyridine amides, and thence to a more general study of nucleophilic substitution in triazolopyridines; we report our results here.



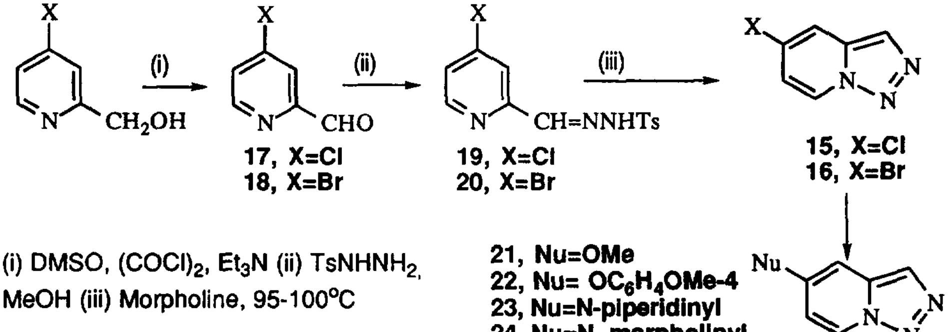
Scheme 1 E = electrophile, Nu = Nucleophile

The amides **3** and **4** were prepared from ethyl triazolopyridine-3-carboxylate[6] via the free acid and acid chloride; the amide **4** is new. We have previously observed[7] that lithiation of amide **3** (LDA, -40°C) with subsequent treatment with bromine, gave a mixture, including only 10% of the desired 7-bromotriazolopyridine **5**. We have subsequently found that dibromotetrachloroethane (DBTCE) is an excellent brominating agent for aryllithiums, and after some experimentation found a procedure (inverse addition, with excess diisopropylamine) which gave bromides **5** and **6** in 52 and 30% yield (in the latter case a substantial amount of amide **4** was always recovered). In earlier experiments we isolated bromide **5** in 24% yield and a second product with two bromine atoms in 39% yield. Analysis and spectral information showed the second product to be the bromopentanoyltriazolopyridine **7**, presumably formed by attack of excess butyllithium on the amide, and bromination of the resulting enolate. This may indicate a more general use for DBTCE as a brominating agent for anions. The reactions between bromoamide **5** and various nucleophiles proceeded as expected, giving compounds **8** to **13** as summarised in Scheme 2. A single experiment with amide **6** gave the methoxy derivative **14**, not isolated pure. A notable feature of reactions between 7-bromotriazolopyridines and secondary amines has been the formation of substantial amounts of pyridine derivatives[4], the parent indeed giving only ring opened products, but the amides showed no tendency to form pyridines. The structures of the substitution products were established by microanalysis and spectroscopy, notably ^{1}H and ^{13}C nmr spectra. All nmr spectra of new triazolopyridines are grouped in Tables 1 and 2.



Scheme 2

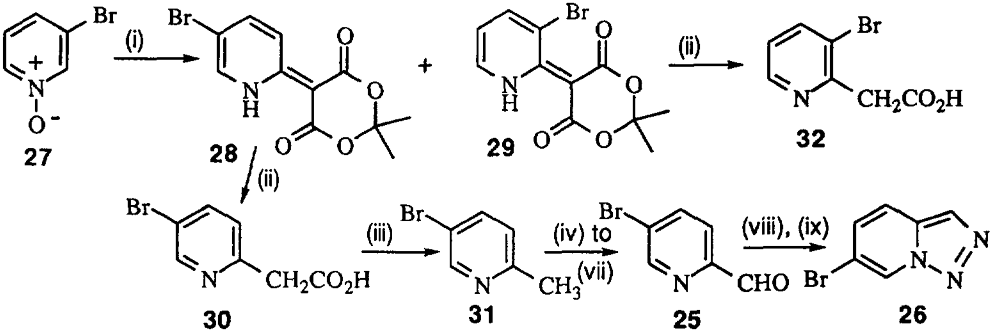
Our interest in the general chemistry of triazolopyridines has led us to synthesize 5- and 6-halogeno derivatives for a brief investigation of their properties. The 5-chloro- **15** and the 5-bromotriazolopyridine **16** were prepared by a lengthy route, as shown in Scheme 3, from 2-picoline *N*- oxide *via* the 4-halogenopyridin-2-yl methanols[8], which were oxidized by Swern's method to the aldehydes **17** and **18**. The tosylhydrazones **19** and **20** were cyclized in morpholine to give compounds **15** and **16** in 71% and 72% yield. The chloro compound **15** was unchanged after 71 hours with sodium *p*-methoxyphenoxide in hot DMF, and no further substitutions were attempted. The bromo compound **16** reacted with sodium methoxide in methanol, with sodium *p* -methoxyphenoxide in hot DMF, and piperidine in ethanol, to give 5-substituted triazolopyridines **21**- **23**. The morpholine derivative **24** was obtained in small yield in the preparation of compound **16**, presumably by reaction between excess morpholine and bromotriazolopyridine **16**. That this cyclisation was nevertheless a satisfactory route to the 5-bromotriazolopyridine is due to the much lower reactivity of the 5-bromo derivative relative to the 7-substituted derivative, reflected in much longer reaction times for the nucleophilic substitutions.



(i) DMSO, $(COCl)_2$, Et_3N (ii) $TsNHNH_2$, MeOH (iii) Morpholine, 95-100°C

Scheme 3

The synthesis of 5-bromopyridine-2-carboxaldehyde **25**, the necessary intermediate for the production of 6-bromotriazolopyridine **26** is more difficult and is summarised in Scheme 4. Bromination of 2-picoline gives a mixture of bromo derivatives[9] and we have examined an alternative, where the methyl group is introduced into 3-bromopyridine *via* the *N* -oxide **27**. Treatment with acetic anhydride and Meldrum's acid gave a mixture of pyridyl Meldrum's acids **28** and **29**, which were easily separated. The required derivative **28**, when heated with concentrated hydrochloric acid, gave 5-bromo-2-pyridylacetic acid, **30**, further decarboxylated by heat to give 5-bromo-2-picoline **31**. Similarly, the compound **29** gave the pyridylacetic acid **32**. From the picoline **31** by a similar sequence to that used for production of compound **18**, the aldehyde **25** and thence, *via* the tosylhydrazone, 6-bromotriazolopyridine **26** was obtained. The 6-bromo derivative proved completely inert to sodium methoxide in methanol with no trace of methoxy compound after 95 hours at the boiling point.

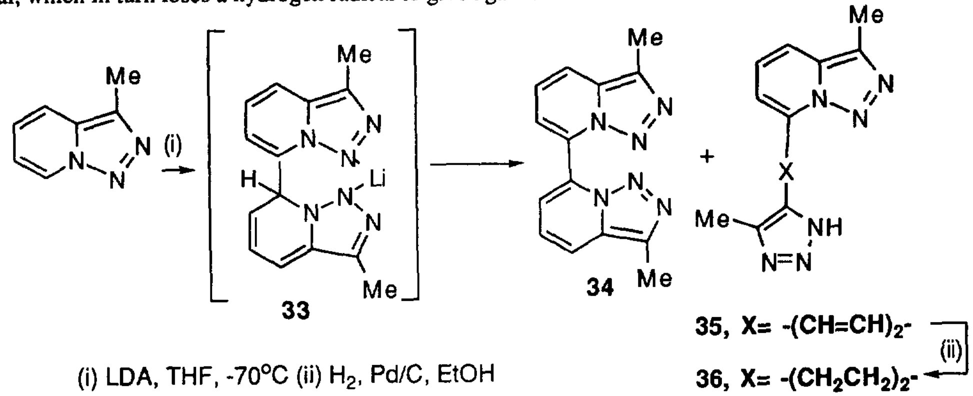


(i) Ac_2O, Meldrum's acid (ii) Conc. aq. HCl, heat (iii) Hydrochloride, 180°C, 33mm Hg
(iv) Peracetic acid (v) Ac_2O (vi) Aq. HCl (vii) Swern oxidation (viii) $TsNHNH_2$, MeOH
(ix) Morpholine, heat

Scheme 4

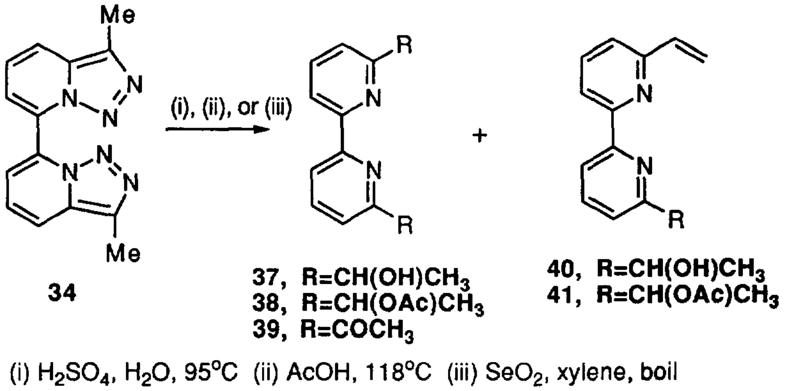
While extrapolation of pyridine properties to predict reactivity in triazolopyridines is often risky, the reactions of the 5-, 6-, and 7-halogenotriazolopyridines do show the expected activation towards nucleophilic substitution at positions 5 and 7, and the benzenoid inertness at position 6. On a qualitative basis the 7-bromo derivatives react much more rapidly than the 5-bromo derivatives; in contrast to the behaviour of 4-chloropyridine is the inertness of 5-chlorotriazolopyridine.

While, as reported above, the usual reaction between triazolopyridine **1** (R=Me) and lithium reagents gives a 7-lithio derivative, trapped by electrophiles, we have now discovered that at -70°C, in THF as solvent, a new reaction occurs, giving two major products. The first and major product (50%) is readily shown by its spectral properties (in particular its mass spectrum, and the ^{1}H nmr spectrum in which the signal for H7 is missing) to be the 7,7'-bitriazolopyridine **34**. The second product (25%) was the butadiene **35**, again identified by microanalysis and spectra. The diene **35** was reduced catalytically to give the 1,4-disubstituted butane **36**. The formation of these products **34** and **35** is explained by the mechanism shown in Scheme 5. Nucleophilic attack at position 7 has been described above; if the anion from **1**(R=Me) is the nucleophile, the intermediate **33** is formed, and this can undergo a known ring opening to give **35** or loss of hydride to give **34**. We have some nmr evidence of the intermediate **33**. Treatment of aliquots from the reaction mixture with D_2O gave a mixture in which signals from starting material and compound **34** could be identified, with additional signals at δ 5.60 (d, J=6.2Hz), 5.85 (dd, J_1=6.2, J_2=9.8Hz), 6.50 (d, J=9.8Hz), which could be assigned to the intermediate **33**. These signals disappeared as the reaction proceeded, being replaced by those of the products. Meth-Cohn *et al.*[10] have suggested an ionic process for the dimerisation of pyridine by LDA, giving an intermediate similar to **33**, but were unable to trap their intermediate. Newkome and Hager[11] have suggested that a radical anion is first involved, this solvated radical ion reacting with a neutral pyridine molecule to give a radical, which in turn loses a hydrogen radical to give again an intermediate similar to salt **33**.



Scheme 5

Since simple triazolopyridines give pyridines when treated with electrophiles[2], we can use compound **34** to produce 2, 2'-bipyridines. These compounds have much use in supramolecular chemistry because of their great complexing power for metal ions[12] and in particular 2,2'-disubstituted-6,6'-bipyridines are useful building blocks for oligo(bipyridines) which spontaneously form helical metal complexes.[13] Reactions to form bipyridines are summarised in Scheme 6. Treatment of compound **34** with aqueous sulphuric acid gave bipyridyl **37** (90%), with hot glacial acetic acid gave bipyridyl **38** (70%), and with selenium dioxide in boiling xylene the bipyridyl **39**(74%). With compounds **37** and **38** were formed small quantities of the elimination products, the vinyl derivatives **40** and **41**. We have thus discovered a general route to 2,2'-bipyridines with a variety of substituents in the 6 and 6' positions; potentially compounds **35** and **36** can also be used to prepare 1-(3-(2-triazolyl)-4-(2-pyridyl) -butadienes and -butanes respectively.



34

37, R=CH(OH)CH$_3$
38, R=CH(OAc)CH$_3$
39, R=COCH$_3$

40, R=CH(OH)CH$_3$
41, R=CH(OAc)CH$_3$

(i) H_2SO_4, H_2O, 95°C (ii) AcOH, 118°C (iii) SeO_2, xylene, boil

Scheme 6

Acknowledgements; Our thanks are due to Rhône-Poulenc Rorer Ltd. for financial assistance (M.A.P.). The work on the reaction of triazolopyridine with LDA and conversion into bipyridyls was supported by the Comision Interministerial de Ciencia y Tecnologia (CICYT Proyect PB94-0959).

EXPERIMENTAL

M.p.s were determined on a heated stage and are uncorrected. Chromatography was performed on a Chromatotron, using 2cm or 4cm plates of silica 60Pf$_{254}$, or for larger amounts, on columns. Elution was by mixtures of petroleum ether b. p. 60-80°C, or hexane, and ethyl acetate. Nmr spectra were recorded on a 60MHz Hitachi-Perkin Elmer R-24B, a Jeol 270MHz EX270, or a Bruker AC250MHz instrument. Ir spectra were recorded for solutions or KBr discs.

N,N-*Diethyl[1,2,3]triazolo[1,5-a]pyridine-3-carboxamide (3)*. - Prepared as described^6 from the acid chloride and diethylamine in 93% yield, b.p. 200-204°C/0.1mmHg, m. p. 31-33°C (lit.^{6} b. p. 200°C/0.2mm Hg, m. p. 31-34°C).

N,N-*Dimethyl[1,2,3]triazolo[1,5-a]pyridine-3-carboxamide (4)*. - Similarly prepared using dimethylamine in 84% yield, m. p. 120-121°C (cyclohexane). (Found: C,56.32; H,5.09; N,29.52. $C_9H_{10}N_4O$ requires C,56.83; H,5.30; N,29.46%). ν_{max}(CHCl$_3$) 1638, 1614cm^{-1}. m/z 190 (M^+, 26.8%), 162 (M^+-N_2, 8.2%), 147 (31.3%), 106 (77.5%), 78 ($C_5H_4N^+$, 100%).

*7-Bromo-*N,N-*diethyl[1,2,3]triazolo[1,5-a]pyridine-3-carboxamide (5)*. -Method a) *n*- Butyllithium (12.85 cm^3, 0.025 mol, 1.96M in hexane), was added to freshly distilled diisopropylamine (3.85 cm^3, 0.027 mol) in a dropping funnel externally cooled to -40°C under argon. The solution was then added dropwise to a stirred solution of amide **3** (5g, 0.023 mol) in anhydrous diethyl ether, (150 cm^3) also at -40°C. After 1h a sample quenched with D_2O showed complete replacement of H7. A solution of DBTCE (8.21g, 0.025 mol) in ether (50 cm^3) was added, the mixture stirred (1h) at -40°C, then allowed to come to room temperature overnight. Hydrolysis with ammonium chloride in ammonia (s.g.0.88), and separation of the organic layer was followed by extraction of the aqueous layer with 100cm^3 portions of CH_2Cl_2, $CHCl_3$, and ethyl acetate. The combined organic layers were dried, ($MgSO_4$), and evaporated, the residue being purified on a column of alumina (activity IV) to give the **amide 5** (3.54g, 52%), m. p. 95°C (petroleum ether b. p. 60-80°C). (Lit.^{6}

m. p. 95°C). Method b) *n* -Butyllithium (10.2 cm^3, 0.02 mol, 1.97M in hexane), was added to freshly distilled diisopropylamine (1.48 cm^3, 0.02 mol) at -40°C under argon. A solution of amide **3** (2g, 0.009 mol) in anhydrous ether (80 cm^3) was added with stirring. When the lithiation was complete (nmr) a solution of DBTCE (6.54g, 0.02mol) in ether (30 cm^3) was added, and the reaction continued as described above. Column chromatography gave first the **bromopentanoyl ketone 7**, (1.9g, 39%), m. p. 118-119°C (ether). (Found: C,36.95; H,3.18; N,12.14. $C_{11}H_{11}Br_2N_3O$ requires C,36.60; H,3.07; N,11.64%). ν_{max} (KBr) 1670cm^{-1}. m/z 363 (M^++4, 11.6%), 361 (M^++2, 25.9%), 359 (M^+, 12.9%), 158 (95%), 156 ($C_4H_3BrN^+$,100%). From later fractions the amide **5** was isolated (0.65g, 24%).

*7-Bromo-*N,N*-dimethyl[1,2,3]triazolo[1,5-a]pyridine-3-carboxamide (6)* .- Using method (a) above on compound **4**, the **bromoamide 6** was isolated in 30% yield, m. p. 173-174°C (petroleum. b.p. 60-80° C)(Found: C,40.34; H,3.45; N,20.58. $C_9H_9N_4Br$ requires C,40.17; H,3.37; N,20.82%). ν_{max} ($CHCl_3$) 1626, 1505 cm^{-1}. m/z 270(M^++2, 21.0%), 268(M^+, 21.5%), 227(39.3%), 225(41.0%), 186(97.4%), 184($C_5H_3BrNCO^+$, 100%), 158(77.7%), 156($C_5H_3BrN^+$, 80.0%).

General Procedures for Nucleophilic substitutions;- a) Alkoxides or thiolates were formed by sodium or sodium hydride in methanol or DMF, and added to the appropriate bromide, dissolved in the same solvent. After the specified period of heating, the solvent was removed under reduced pressure, the residue treated with water and extracted with dichloromethane, and after evaporation purified by crystallisation or Chromatotron.

b) For amines, the bromoamide was dissolved in the neat amine and heated at the specified temperature. Work-up was as described above but saturated $NaHCO_3$ was used instead of water.

*7-Phenylthio-*N,N*-diethyl[1,2,3]triazolo[1,5-a]pyridine-3-carboxamide (8).* - Prepared in DMF at 95°C, (17h), in 78% yield, the **phenylthio derivative 8** was purified by Chromatotron followed by recrystallisation from cyclohexane, m. p. 92-93°C. (Found: C. 62.33; H, 5.66; N, 17.01. $C_{17}H_{18}N_4OS$ requires C, 62.55; H, 5.56; N, 17.16%). m/z 227 (M^+-C_5H_9NO, 73.8%), 226(M^+-$C_5H_{10}NO$, 100%).

*7-Anisyloxy -*N,N*-diethyl[1,2,3]triazolo[1,5-a]pyridine-3-carboxamide (9)* .- Prepared in DMF at 95°C, (17h), in 64% yield, the **anisyloxy derivative 9** was purified by recrystallisation from cyclohexane, m. p. 105-106°C. (Found: C, 63.73; H, 6.00; N, 16.69. $C_{18}H_{20}N_4O_3$ requires C, 63.52; H, 5.92; N, 16.46). m/z 241 (M^+- C_5H_9NO,54.7%), 226, (100%).

*3-*N,N*-Diethylcarbamoyl[1,2,3]triazolo[1,5-a]pyridin-7-ylhydrazine (10).* - Prepared in hydrazine hydrate (90°C, 22h) in 36% yield, the **hydrazine 10** was purified by recrystallisation from ethyl acetate, m. p. 166-167°C. (Found: C, 53.30; H, 6.31; N, 33.61. $C_{11}H_{16}N_6O$ requires C, 53.21; H, 6.50; N, 33.85%). m/z 149(26.1%, M^+- C_5H_9NO).

7-(N*-Piperidinyl)-* N,N*-diethyl[1,2,3]triazolo[1,5-a]pyridine-3-carboxamide (11)* .- Prepared in ethanolic piperidine (boiled 24h) and purified by Chromatotron, followed by recrystallisation from cyclohexane,in 65% yield, the **piperidinyl derivative 11** had m. p. 80-81°C. (Found: C, 64.04; H, 7.75; N, 23.30. $C_{16}H_{23}N_5O$ requires C, 63.76; H, 7.69; N, 23.24%). m/z 301 (M^+, 5.9%), 273 (M^+-N_2, 21.9%), 202 (M^+- C_5H_9NO, 79.5%), 161 ($C_{10}H_{13}N_2^+$, 100%). 27% of starting material was recovered.

7- (N*-Morpholinyl) -* N,N*-diethyl[1,2,3]triazolo[1,5-a]pyridine-3-carboxamide (12)*. -Prepared in morpholine (90-100°C, 30h), and purified by Chromatotron and recrystallisation from cyclohexane in 80% yield, m. p. 109-110°C. (Found: C, 59.36; H, 6.96; N, 23.20. $C_{15}H_{21}N_5O_2$ requires C, 59.39; H, 6.98; N, 23.09%).

7-(4-Methylpiperazin-1-yl)-*N,N*-diethyl[1,2,3]triazolo[1,5-a]pyridine-3-carboxamide (13).- Prepared in N-methylpiperazine (90-100°C, 18h) and purified by recrystallisation from cyclohexane, in 56% yield, m. p. 113-114°C. (Found: C, 60.65; H, 7.36; N. 26.39. $C_{16}H_{24}N_6O$ requires C, 60.74; H, 7.65; N, 26.56%). m/z 316(M$^+$, 10.8%), 176 ($C_{10}H_{14}N_3^+$, 100%).

7-Methoxy -N,N-dimethyl[1,2,3]triazolo[1,5-a]pyridine-3-carboxamide (14).- Prepared in methanol; identified only by methoxyl signal.

TABLE 1 ^{1}H Nmr Shifts (ppm) and J Values (Hz) for Triazolopyridines

Compound	H3	H4	H5	H6	H7	Other	J values (Hz)
3[a]		8.39d	7.39dd	6.92dd	8.73d	3.3-4.3m(2xCH_2);1.27t(2xCH_3)	$J_{4,5}=9;J_{5,6}=7;J_{6,7}=7$
4[a]		8.29d	7.36dd	7.00dd	8.65d	3.29brs(CH_3); 3.66brs (CH_3)	$J_{4,5}=9;J_{5,6}=7;J_{6,7}=7$
5[b]		8.47m	<7.35-7.41m>			4.13q(CH_2); 3.64q(CH_2); 1.41t (CH_3); 1.31q(CH_3)	
6[a]		8.18-8.50m	<7.10-7.45m>			3.61brs(CH_3); 3.16brs(CH_3)	
7[b]		8.54d	<7.49-7.63m>			5.75-5.80m (CH); 2.04-2.29m (CH_2);1.41-1.69m(CH_2); 0.98-1.04t(CH_3)	$J_{4,5}=8.55$
8[a]		8.20d	d	6.39d		7.05-7.80m(Ph+H5); 3.30-4.40m (2xCH_2);1.32t(2xCH_3)	$J_{4,5}=9$; $J_{5,6}=7$
9[a]		8.02d	d	6.06d		6.73-7.31m(C_6H_4+H5); 3.78s (CH_3); 3.30-4.30m(2xCH_2); 1.28t(2xCH_3)	$J_{4,5}=9$; $J_{5,6}=7$
10[b]		7.75d	d	6.59d		7.34-7.46m(NH+H5);4.07-4.10m (NH2+CH_2);3.60-3.63 m (CH_2); 1.29-1.36m (2xCH_3)	$J_{4,5}=8.66$; $J_{5,6}=7.45$
11[a]		8.05d	7.38dd	6.36d		3.30-4.40m(4xCH_2); 1.71-2.10brs (3xCH_2); 1.39t(2xCH_3)	$J_{4,5}=9$; $J_{5,6}=7$
12[a]		8.06d	7.38dd	6.35d		3.85-4.45m(3xCH_2); 3.40-3.70m (3xCH_2); 1.38t(2xCH_3)	$J_{4,5}=9$; $J_{5,6}=7$
13[b]		8.10d	7.41dd	6.41d		4.12m(CH_2); 3.50-3.70m (3xCH_2); 2.60-2.70m(2xCH_2); 2.40s(CH_3) and1.30s(CH_3)	$J_{4,5}=8.8$; $J_{5,6}=7.33$
15[a]	7.90s	7.61d		6.83dd	8.55d		$J_{4,6}=1$; $J_{6,7}=7$
16[b]	8.22s	8.32d		7.33dd	9.10d		$J_{4,6}=2.22$; $J_{6,7}=7.44$
22[b]	7.80s	6.76d		6.85dd	8.66d	7.08d(2xCH); 6.97d(2xCH); 3.85s(CH_3)	$J_{4,6}=2.22$; $J_{6,7}=7.55$
23[b]	7.71s	6.69-6.75m		6.69-6.75m	8.48d	3.20-3.24m(2xCH_2); 1.61-1.72m (3xCH_2)	$J_{6,7}=7.65$
24[b]	7.79d	6.74-6.76m		6.74-6.76m	8.56dd	3.87-3.90m(2xCH_2); 3.22-3.26m (2xCH_2)	$J_{3,7}=0.98$; $J_{6,7}=8.79$
26[b]	8.08s	7.68d	7.32dd		8.91d		$J_{4,5}=9.28$; $J_{5,7}=1.5$
34[c]		7.72dd	7.28dd	7.80dd		2.61(6H,s)	$J_{4,5}=8.8$; $J_{5,6}=6.9$; $J_{4,6}=1.1$
35[c]		7.44d	e	6.90d		7.84(1H, dd); 7.15-7.08(3H, m); 6.70(1H, d); 2.58(3H, s); 2.37 (3H, s);	$J_{4,5}=8.4$; $J_{5,6}=6.9$; $J_{cis}=10.9$, $J_{trans}=15.5$
36[c]		7.40d	7.06dd	6.63d		3.16(2H,t); 2.64(2H,t); 2.51(3H, s); 2.19(3H, s);1.85-1.73(4H,m); 10.5(1H, s, NH)	$J_{4,5}=8.8$; $J_{5,6}=6.6$

[a] 60MHz, [b] 270MHz, [c] 250MHz; all spectra in $CDCl_3$ except **16** (dmso-d_6) ; [d] H5 under C_6H_5 signal;
[e] Multiplet at δ 7.15-7.08 (3H) includes H5.

TABLE 2 ^{13}C Nmr Shifts of Triazolopyridines (ppm)

Compound	C3	C3a	C4	C5	C6	C7	Other
3[a]	135.73	133.13	120.65	127.31	116.03	124.91	160.90,43.05, 41.25, 14.69,12.96
4[b]	135.75	133.08	120.53	127.47	116.13	124.98	161.89, 38.81, 36.21
5[b]	137.53	134.70	120.53	128.35	119.85	115.24	160.93, 43.31, 41.50, 14.73, 12.97
6[b]	137.37	134.51	120.61	128.13	120.36	115.24	161.63, 38.86, 36.62
7[b]	118.74	136.72	121.54	131.58	118.77	116.93	188.46, 48.38, 35.42, 20.74, 13.54
8[a]	136.54	133.57	116.68	127.81	113.56	127.50	161.27, 138.29, 135.59,130.45, 130.23, 43.28, 41.43, 14.74, 13.04
9[a]	137.78	133.49	113.36	129.40	96.62	146.68	161.35, 157.76, 149.11, 121.7, 115.31, 55.68, 43.25, 41.40, 14.72, 13.04
10[b]	136.31	132.71	107.47	130.41	92.65	143.38	161.69, 42.30, 41.31, 14.73, 13.05
11[a]	137.66	132.83	112.41	129.30	101.08	145.82	161.61, 50.59, 43.23, 41.35, 25.59, 24.37, 14.68, 13.04
12[a]	137.63	133.04	113.32	129.20	100.89	144.59	161.40, 66.52, 49.49, 43.20, 41.36, 14.80, 13.02
13[b]	137.67	132.94	112.91	129.22	101.03	144.90	161.50, 54.60, 49.09, 46.13, 43.20, 41.34, 14.81, 13.03
15[b]	125.82	133.88	116.85	131.76	116.58	125.33	
16[b]	125.23	134.22	120.22	118.54	118.92	126.57	
22[b]	124.66	134.75	110.36	147.47	98.45	126.40	157.29, 151.17, 121.95, 115.33, 55.72, 43.14, 41.3, 14.71, 13.01
23[b]	124.98	135.47	109.74	148.85	95.53	123.00	49.49, 25.26, 23.99
24[b]	125.44	135.17	109.01	148.45	96.21	123.61	66.43, 48.52
26[b]	125.36	132.22	118.30	128.98	110.64	126.19	
34[c]	132.40	128.40	118.93	123.30	118.33	135.34	10.30
35[c]	132.40	130.32	115.48	124.22	114.26	134.13	136.19, 134.79, 122.44, 122.15, 116.32, 115.92, 8.50, 7.75
36[c]	131.90	134.44	114.86	123.88	112.92	138.20	142.31, 139.00, 30.20, 28.43, 25.50, 23.61, 10.26, 9.26

[a] = 23MHz [b]= 68MHz [c]=62.9MHz; all spectra in $CDCl_3$ except **16** (dmso-d_6) and**35** (CD_3OD)

***4-Chloropyridine-2-carboxaldehyde** (17)*;- A solution of DMSO (1.7 cm^3, 24 mmol) in anhydrous dichloromethane (10 cm^3) was added dropwise to a stirred solution of oxalyl chloride (1.05 cm^3, 12mmol) in anhydrous dichloromethane (25 cm^3) under N_2 at -50 to -60°C. After 2 min 4-chloropyridine-2-methanol (1.5g, 10.45 mmol) in dichloromethane (10 cm^3) was added over 5 min, and stirring continued (15 min). Triethylamine (7.29 cm^3, 52.30mmol) was added and the reaction mixture stirred (5 min) before being allowed to warm to room temperature. Water (35 cm^3) was added, the organic layer separated, and the aqueous layer extracted with dichloromethane. The combined organic layers were washed with saturated sodium chloride, water, 5% sodium carbonate, and again with water, dried ($MgSO_4$) and evaporated to give the aldehyde **17** as a yellow oil (1.0g, 68%). B. p. 78-80°C at 0.2 mm Hg (lit.[8] b. p. 80-83°C at 3mm Hg). From the aldehyde **17** and tosylhydrazine in methanol was obtained the crystalline **tosylhydrazone 19** m. p. 108-112°C (65%). (Found: C, 50.16; H, 3.85; N, 13.77. $C_{13}H_{12}ClN_3O_2S$ requires C,50.40; H, 3.88; N, 13.57%). ^1H nmr (60MHz, $CDCl_3$) δ 11.90(1H, brs, NH), 8.27(1H, d, H6, $J_{6,5}$=5Hz), 7.65-7.75(4H, m), 7.05-7.25 (3H, m), 2.35(3H, s, CH_3). ^{13}C nmr δ(23MHz, d_6-dmso) 153.88(C2), 150.59 (CH), 145.05 (CH, C6), 143.49 (C1'), 143.39 (C4), 135.87 (C4'), 129.61 (CH, C2' and C6'), 127.05 (CH, C3' and C5'), 121.11 (CH, C3), 119.03 (CH, C5), 21.02 (CH_3).

5-Chloro[1,2,3]triazolo[1,5-a]pyridine (15);- A solution of the tosylhydrazone **19** (1g, 3.23 mmol) in morpholine (6 cm^3) was heated and stirred at 90-100°C (2h). The excess morpholine was removed *in vacuo* and the resulting yellow solid treated with ether, filtered to remove morpholine toluenesulphinate, and the filtrate evaporated to give **5-chlorotriazolopyridine 15** as colourless crystals (from cyclohexane) m. p. 92-98°C (0.35g, 71%). (Found: C,46.88; H, 2.46; N, 26.96. $C_6H_4ClN_3$ requires C, 46.90; H, 2.61; N, 27.36%). m/z 155(M^++2, 12.6%), 153(M^+, 39.1), 127(32.5%), 125(M^+-N_2, 99%), 90(100%).

4-Bromo-2-pyridylmethanol ;- a) A solution of 4-bromo-2-picoline *N* -oxide[14] (5g, 26.6 mmol) in acetic anhydride (50 cm^3) was stirred and heated at 100°C in the dark (1h). Excess acetic anhydride was removed by fractional distillation to give **4-bromo-2-pyridylmethanol acetate** as a colourless oil b. p. 78-80°C at 0.03mm Hg (4.11g, 67%). (Found: C,41.05; H,3.53; N, 6.36%. $C_8H_8BrNO_2$ requires C, 41.77; H, 3.50; N, 6.09%). m/z 231 (M^++2, 2.9%), 229(M^+, 2.8%). b) A solution of the acetate (7.72g, 33.56 mmol) in hydrochloric acid (10%, 100cm^3) was stirred and heated at 80°C in the dark (16h). The cooled solution was neutralized with potassium carbonate, the product extracted with chloroform and dried ($MgSO_4$). Evaporation and distillation gave **4-bromo-2-pyridylmethanol** as a colourless oil, b. p. 100-105°C at 0.5mm Hg (5.93g, 94%). (Found: C, 38.24; H, 3.26; N, 7.37. C_6H_6BrNO requires C, 38.33; H, 3.22; N, 7.45%). m/z 189(M^++2, 55.9%), 187(M^+,62.9%). ^1H nmr δ (270 MHz, $CDCl_3$) 8.31 (1H, d, H6, J=5.2Hz), 7.57 (1H, d, H3, $J_{3,5}$ = 1.46Hz), 7.36 (1H, dd, H5, J5,3 = 1.46, J5,6 = 5.2Hz), 4.74 (3H, br, CH_2OH). ^{13}C nmr (68 MHz, $CDCl_3$) 161.64 (C2), 149.29 (CH, C6), 133.85 (C4), 125.73 (CH, C3), 124.18 (CH, C5), 64.01 (CH_2).

4-Bromopyridine-2-carboxaldehyde (18);- Prepared from the bromo-alcohol as described for compound **17** in 86% yield, the aldehyde **18** was converted into the **tosylhydrazone 20**, m. p. 118-124°C (from methanol) in 66% yield. (Found: C, 43.91; H, 3.44; N, 11.85%. $C_{13}H_{12}BrN_3O_2S$ requires C, 44.08; H, 3.41; N, 11.86%). ^1H nmr δ (270 MHz, d_6-dmso) 12.12 (1H, br s, H10), 8.46 (1H, d, H6, J = 5.19Hz), 8.03 (1H, s, CH=N), 7.89-7.92 (3H, m, H3, H2' and H6'), 7.60 (1H, dd, H5, $J_{5,6}$ = 5.19Hz), 7.45 (2H, d, H3' and H5'), 2.37 (3H, s, CH_3). ^{13}C nmr δ (68 MHz, d_6-dmso) 153.95 (C5), 150.57 (CH, C6), 145.26 (CH, CH=N), 143.72 (C1'), 136.12 (C4'), 132.67 (C4), 129.80 (CH, C2' and C6'), 127.27 (CH, C3' and C5'), 127.19 (CH, C3), 122.28 (CH, C5), 21.04 (CH_3).

5-Bromo-[1,2,3]triazolo[1,5-a]pyridine (16);- Prepared as for compound **15** from tosylhydrazone **20** , and purified by Chromatotron. The **5-bromo-[1,2,3]triazolo[1,5-a]pyridine 16** was first eluted, in 72% yield, m. p. 130-131°C (cyclohexane). (Found: C, 36.37; H, 1.91; N, 21.04. $C_6H_4BrN_3$ requires C, 36.39; H, 2.04; N, 21.22%). m/z 199 (M^++2, 23.4%), 197(M^+, 25.2%), 169 M^+-N_2, 41.2%), 90 (M^+-(N_2+Br), 100%) . Thesecond product was the 5-morpholinyl derivative, **24**, (5%), m.p. 110-112° C (cyclohexane), m/z 204 (M^+, 25.9%), 118(100%).

5-Methoxy[1,2,3]triazolo[1,5-a]pyridine (21)..- Prepared in methanol (boiling, 89h) in 66% yield, purified by Chromatotron and recrystallisation from cyclohexane m. p. 99-100°C (lit.[6] m. p. 99-101°C); 34% of starting material was recovered.

5-Anisyloxy[1,2,3]triazolo[1,5-a]pyridine (22) .- Prepared in DMF (100°C, 189h), purified by Chromatotron and recrystallisation from cyclohexane, in 25% yield, m. p. 160-163°C. m/z 241 (M+, 26.9%).

5-N-piperidinyl[1,2,3]triazolo[1,5-a]pyridine (23) . - Prepared in piperidine (boiled, 64h) and purified by Chromatotron and recrystallisation from cyclohexane, in 49% yield, m. p. 99-101°C. m/z 202 (M+, 100%).

Reaction of 3-bromopyridine-N-oxide (27) with Meldrum's Acid;- A solution of Meldrum's acid (14.4g, 0.1 mol) in acetic anhydride (100 cm^3) was stirred and cooled in an ice/water bath, and 3-bromopyridine-*N*-

oxide[15] (17.4g, 0.1mol) was added slowly, keeping the reaction temperature below 5°C. The stirred mixture was allowed to come to room temperature overnight. The crude product was filtered and the filtered yellow crystals treated with warm chloroform. The insoluble material crystallized from acetonitrile as yellow crystals of the **3-bromo-2-pyridylidene Meldrum's acid 29**, m. p. 188-190°C (1.65g, 6%). (Found: C, 43.90; H, 3.14; N, 4.69. $C_{11}H_{10}BrNO_4$ requires C, 44.02; H, 3.36; N, 4.67%). The chloroform filtrate was evaporated and the residue crystallized from methanol to give **5-bromo-2-pyridylidene Meldrum's acid 28** , colourless crystals, m. p. 265-268°C (7.48g, 25%). (Found: C, 43.84; H, 3.24; N, 4.51. $C_{11}H_{10}BrNO_4$ requires C, 44.02; H, 3.36; N, 4.67%). ^{1}H nmr (270 MHz, d$_6$-dmso), δ 14.93 (1H, brs, NH), 8.66 (1H, d, H3, $J_{3,4}$=9.4Hz), 8.54 (1H, d, H6, $J_{6,4}$=2.13Hz), 8.23 (1H, dd, H4, J=2.6 and 9.8Hz), 1.64 (6H, s, 2xCH_3).

5-Bromo-2-pyridylacetic Acid (30). - A solution of compound **28** (5g, 16.66 mmol) in conc. hydrochloric acid (50 cm^3) was boiled under reflux (2h). The solution was evaporated and the residue crystallized from water to give the **acid 30** m. p. 145-147°C (2.98g, 83%). (Found: C, 38.88; H, 2.72; N, 6.47. $C_7H_6BrNO_2$ requires C, 38.92; H, 2.80; N, 6.48%). m/z 173 (M$^+$+2, 95%), 171(M$^+$,100%).

3-Bromo-2-pyridylacetic Acid (32). - Prepared as for compound **30**, the acid **32** hydrochloride in 80% yield. The **methyl ester** had b. p. 80-83°C at 0.025mm Hg(Found: C, 41.81; H, 3.44; N, 6.00. $C_8H_8BrNO_2$ requires C, 41.77; H, 3.50; N, 6.09%).

5-Bromo-2picoline (31). - Sublimation of the hydrochloride of acid **30** at 180°C/33mm Hg gave a white solid, which when treated with aqueous $NaHCO_3$ gave the bromopicoline **31** (61%), m. p. 34-35°C (lit.[9] m. p. 32-33°C).

5-Bromopyridine-2-carboxaldehyde (25) .- Prepared from 5-bromo-2-methylpyridine-*N*-oxide via the 5-bromopyridine-2-methanol acetate[16], which was hydrolysed as described above in 79% yield to give **5-bromopyridine-2-methanol**, b. p. 120°C at 0.06mm Hg, m. p. 52-54°C. m/z 189(M$^+$+2, 77.7%), 188(96%), 187(M$^+$, 81.8%), 186(M$^+$-1, 94.3%), 160(77.8%), 158(M$^+$-CHO, 100%). ^{1}H nmr (270 MHz, $CDCl_3$) δ 8.62 (1H, d, H6, $J_{6,4}$=2.2Hz), 7.82 (1H, dd, H4, $J_{4,6}$=2.2Hz, $J_{4,3}$=8.3Hz), 7.22(1H, d, H3, $J_{3,4}$=8.43Hz), 4.73(2H, s, CH_2), 3.49(1H, brs, exch. D_2O, OH). The alcohol was oxidized (Swern) as described above for compound **17**, to give the aldehyde **25** in 75% yield, b. p. 65-70°C at 26mm Hg, m. p. 78-80°C (lit.[16] m. p. 85-87°C). (Found: C, 38.72; H, 2.05; N, 7.54. Calc. for C_6H_4BrNO; C, 38.74; H, 2.17; N, 7.53%). The **tosylhydrazone** prepared in 87% yield, had m. p. 141-144°C (methanol). (Found: C, 44.27; H, 3.36; N, 11.96. $C_{13}H_{12}BrN_3O_2S$ requires C, 44.08; H, 3.41; N, 11.86%). ^{1}H nmr δ(270 MHz, d$_6$-dmso) 8.69 (1H, d, H6, $J_{6,4}$ = 2.08Hz), 8.06 (1H, dd, H4, $J_{4,6}$ = 2.08 and $J_{4,3}$ = 8.5Hz), 7.96 ((1H, s, CH=N), 7.86 (2H, d, H2' and H6'), 7.76 (1H, d, H3, J = 8.5Hz), 7.44 (2H, d, H3' and H5'), 3.55 (1H, br s, NH), 2.37 (3H, s, CH_3). ^{13}C nmr δ (68 MHz, d$_6$-dmso) 151.24 (C2), 150.12 (CH, C6), 145.71 (CH, CH=N), 143.64 (C1'), 139.52 (CH, C4), 136.01 (C4'), 129.74 (CH, C2' and C6'), 127.19 (CH, C3' and C5'), 121.10 (CH, C3), 120.79 (C5), 20.98 (CH_3).

6-Bromo[1,2,3]triazolo[1,5-a]pyridine (26) ;- Prepared from the tosylhydrazone as described for compound **16** in 83% yield, m.p. 93-95°C (cyclohexane). (Found: C, 36.36; H, 1.91; N, 20.97. $C_6H_4BrN_3$ requires C, 36.39; H, 2.04; N, 21.22%). m/z 199(M$^+$+2, 16%), 197 (M$^+$, 16%), 90 (M$^+$-(Br+N_2), 58.2%), 63(100%).

7,7' -Bi(3-methyl[1,2,3]triazolo[1,5-a]pyridine) (34) and ***1- (3-Methyl[1,2,3]-triazolo[1,5-a]pyridin-7-yl)-4-(5-methyl-1H-[1,2,3]triazol-4-yl)-1,3-butadiene- (35)*** . -A solution of *n* -butyllithium in hexane (9.4cm^3, 1.6M) was added to diisopropylamine, freshly distilled from KOH (2cm^3, 15mmol) at -70°C, under argon. A solution of **I (R=Me)** (2g, 15mmol) in anhydrous THF (80cm^3) was added with stirring. A deep red colour developed. The mixture was kept at -70°C (9h) and then at room temperature (48h), during which time the solution became yellow. Hydrolysis with ammonium chloride/aqueous ammonia (s.g. 0.880), then acidification and extraction with dichloromethane gave, after drying and evaporation of the organic solvent, a residue (2g) which was purified by chromatography on silica gel. Elution with hexane/ethyl acetate (3:7) gave starting material (0.6g). Further elution (1:4) gave the **butadiene 35**, as a deep yellow solid, m.p. 210-212°C (ethanol) (0.35 g, 25% on unrecovered starting material). HPMS found for M^+ 266.1281; $C_{14}H_{14}N_6$ requires 266.1280. λ_{max} ($\log_{10}\varepsilon$) (EtOH) 371(4.41), 358(3.40), 283(4.23),and 222(4.36)nm. Further elution produced the yellow **compound 34**, m.p.238-240°C (ethyl acetate/hexane) (0.70g, 50% on unrecovered starting material). HPMS found for M^+ 264.1116; $C_{14}H_{12}N_6$ requires 264.1123. λ_{max} ($\log_{10}\varepsilon$) (EtOH) 337(3.68), 281(3.57), and 225(4.12)nm.

1-(3-Methyl[1,2,3]triazolo[1,5-a]pyridin-7-yl)-4-(5-methyl-1*H*-[1,2,3]triazol-4-yl)-butane-(36).- Hydrogenation of compound **35** in ethanol with Pd/C catalyst gave the **tetrahydro derivative** (**36**) in 85% yield. HPMS found for M^+ 270.1596 ; $C_{14}H_{18}N_6$ requires 270.1593.

6,6'-Di(1-hydroxyethyl)-2,2'-bipyridine (37) and ***6- (1-hydroxyethyl)-6'-vinyl-2,2'-bipyridine (40).*** - A solution of compound **34** (250mg, 0.95mmol) in sulphuric acid (20cm^3, 2.5M) was boiled (8h), cooled, neutralized (aq. $NaHCO_3$), and extracted with dichloromethane. The organic layers were dried, filtered, and evaporated, and the crude residue purified by chromatography (hexane/ethyl acetate, 1:1, then increasing ethyl acetate). First from the column was the **vinyl derivative 40** (10mg, 4%). HPMS found for M^+ 226.1107; $C_{14}H_{14}N_2O$ requires 226.1106). ^{1}H nmr (250MHz, $CDCl_3$) δ 8.38(1H, d, J=7.7Hz), 8.25(1H, d, J=8.0Hz), 7.78(1H, dd, J_1=7.7, J_2=8.0Hz), 7.73(1H, dd, J_1=7.7, J_2=8.0Hz), 7.30(1H, d, J=7.7Hz), 7.22(1H, d, J=7.7Hz), 6.48(1H, dd, J_{cis}=10.9, J_{trans}=17.3Hz), 6.30(1H, dd, J_{trans}=17.3Hz, J_{gem}=1.4Hz), 5.47(1H, J_{cis}=10.9, J_{gem}=1.4Hz), 4.90(1H, q, J=6.6Hz), 4.70(1H, br s, OH), 1.50(3H, d, J=6.6Hz). Subsequently eluted was compound **37** which had m.p.94-110°C , (207 mg, 90%).HPMS found for M^+ 244.1216; $C_{14}H_{16}N_2O_2$ requires 244.1212. ^{1}H nmr (250 MHz, $CDCl_3$) δ 8.27(2H, d, J=8.0Hz, H3/H3'), 7.76(2H, dd, J_1=7.7, J_2=8.0Hz, H4/H4'), 7.22(2H, d, J=7.7Hz, H5, H5'), 4.89(2H, q, J=6.6Hz, C*H* OH), 4.49(2H, s, OH), 1.48(6H, d, J=6.6Hz, C*H*$_3$CH(OH)).

6,6'-Di(1-acetoxyethyl)-2,2'-bipyridine (38) and***6- (1-acetoxyethyl)-6'-vinyl-2,2'-bipyridine (41).*** - A solution of compound **34** (208mg, 0.79mmol) in glacial acetic acid (10 cm^3) was boiled (30 min), evaporated, and worked up as for compound **37**. Chromatography of the crude product gave two products. First from the column was the **vinyl derivative 41**, as an oil, (22mg, 10%). HPMS found for M^+ 268.1207 ; $C_{16}H_{16}N_2O_2$ requires 268.1212. ^{1}H nmr (250MHz, $CDCl_3$) δ 8.35(1H, d, J=8.0Hz), 8.27(1H, d, J=8.0Hz), 7.72(1H, dd, J_1=7.7, J_2=8.0Hz), 7.68(1H, dd, J_1=7.7, J_2=8.0Hz), 7.27(1H, d, J=7.7Hz), 7.23(1H, d, J=7.7Hz), 6.81(1H, dd, J_{cis}=10.5, J_{trans}=17.4Hz), 6.27(1H, dd, J_{trans}=17.4, J_{gem}=1.4Hz), 5.43(1H, dd, J_{cis}=10.5, J_{gem}=1.4Hz), 5.95(1H, q, J=6.6Hz), 2.10(3H, s), 1.60(3H, d, J=6.6Hz). The second compound eluted was the diacetoxy compound **38**, m.p. 70-78°C, (180mg, 70%), previously reported as a pure enantiomer[17]. HPMS found for M^+ 328.1413 ; $C_{18}H_{20}N_2O_4$ requires 328.1423). ^{1}H nmr (250MHz, $CDCl_3$) δ 8.29(2H, dd, J_1=6.9, J_2=1.0Hz, H3, H3'), 7.72(2H, dd, J_1=6.9, J_2=7.7Hz, H4, H4'), 7.27(2H, dd, J_1=7.7, J_2=1.0Hz, H5, H5'), 5.94(2H, q, J=6.6Hz), 2.07(6H, s), 1.58(6H, d, J=6.6Hz).

6,6'-Diacetyl-2,2'-bipyridine (39) ;- A solution of compound **34** (250mg, 0.95mmol) in xylene (40cm^3) with selenium dioxide (420mg) was boiled (1h), filtered and evaporated. The residue was treated with water and dichloromethane, the organic layer dried, filtered, and evaporated to give the diacetylbipyridine **39** crystallized from ethanol, m.p. 177-179°C (lit.[18] m.p. 178.5-179.5°C)(170mg, 74%). HPMS found for M^+ 240.0891; $C_{14}H_{12}N_2O_2$ requires 240.0898. ν_{max} (KBr) 1700 cm^{-1}. ^1H nmr (250MHz, $CDCl_3$) δ 8.68(2H, d, J=7.8Hz, H3/H3'), 8.04(2H, d, J=8.0Hz, H5/H5'), 7.96(2H, dd, J_1=7.8, J_2=8.0Hz, H4/H4'), 2.79(6H, s, CH_3CO). ^{13}C nmr (62.9 MHz, $CDCl_3$) 200.07 (C=O), 154.56 (C2), 152.95 (C6), 137.93 (CH, C4), 124.30 (CH, C3), 121.85 (CH, C5), 25.76 (CH_3).

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