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TRIAZOLOPYRIDINES. PART 8.[1] NUCLEOPHILIC SUBSTITUTION REACTIONS OF 5-BROMO[1,2,3]TRIAZOLO[5,1-a]ISOQUINOLINE AND 7-BROMO[1,2,3]-TRIAZOLO[1,5-a]PYRIDINE

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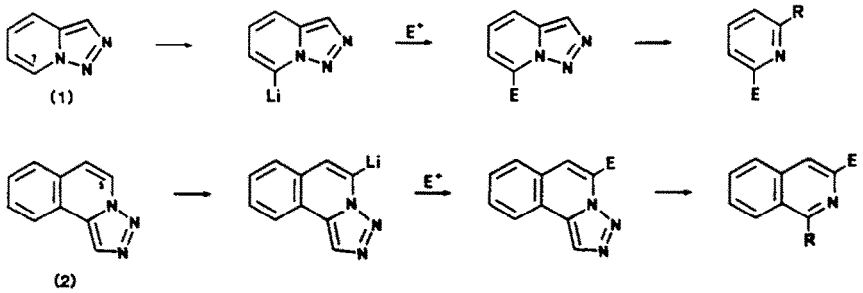
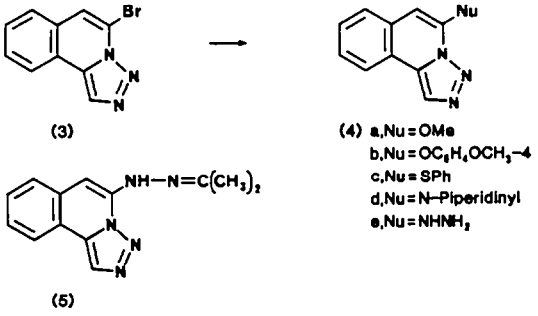
Abstract. Nucleophilic substitution of 5-bromotriazoloisoquinoline (3) and of 7-bromo-3-methyltriazolopyridine (6) proceeds readily to give a range of 5-substituted triazoloisoquinolines (4a)-(4e), and of 7-substituted triazolopyridines (7a)-(7h) respectively. Triazoloisoquinolines have been converted into 1,3-disubstituted isoquinolines (11)-(13), (15), and (16), and triazolopyridines into 2,6-disubstituted pyridines (17)-(19). Of secondary amine nucleophiles, only piperidine reacted with 7-bromo-3-methyl-triazolopyridine (6) to give the 7-substituted derivative (7g). A second product in this reaction was a 2,6-disubstituted pyridine (8); the similar compounds (20)-(24) were the only products when morpholine or N-acetyl-piperazine were used. The reaction between 7-bromotriazolopyridine (9) and piperidine or morpholine gave in high yield the 2,6-disubstituted pyridines (25) and (26).

We have reported[2-4] that triazolopyridine (1) and triazoloisoquinoline (2) can be regiospecifically lithiated; subsequent reaction with electrophiles give respectively 7-substituted triazolopyridines and 5-substituted triazoloisoquinolines. Since we have also discovered methods to open the five membered rings with loss of nitrogen[5] the overall process is the equivalent of a regiospecific synthesis of 2,6-disubstituted pyridines or of 1,3-disubstituted isoquinolines by electrophilic attack on the 2-substituted pyridine or 1-substituted isoquinoline. If the synthesis were to be completely general it would require a method to introduce nucleophiles into the triazolo-pyridine or -isoquinoline. We have now achieved this generality, by using 7-bromotriazolopyridines or 5-bromotriazoloisoquinoline.[6]



The key to the introduction of nucleophiles was an efficient synthesis of 5-bromotriazoloisoquinoline (3) and 7-bromo-3-methyltriazolopyridine (6) from the corresponding lithio derivatives by using 1,2-dibromo-1,1,2,2-tetrachloroethane.[1] We describe the reactions of the bromotriazoloisoquinoline first because they are simpler. A preliminary experiment using sodium methoxide in boiling methanol showed that the bromine in compound (3) was slowly replaced (50% complete in 20 hours) to give the 5-methoxy derivative (4a). The upfield shift of the singlet due to H6 to δ6.25 was characteristic. Reaction between compound (3) and sodium 4-methoxyphenoxide in boiling DMF gave the 5-(4-methoxyphenoxy) derivative (4b). Similar reaction with sodium thiophenoxide gave the 5-phenylthio derivative (4c) in poor yield. Boiling piperidine converted the bromotriazoloisoquinoline (3) into the 5-piperidino derivative (4d), and hydrazine hydrate at 100°C gave the triazoloisoquinolyl hydrazine (4e) both in excellent yield. The hydrazine (4e) was characterized as its condensation product with acetone (5).

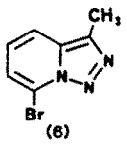


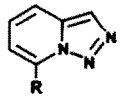
(3)

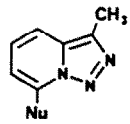
(4) a,Nu = OMe
b,Nu = $OC_6H_4OCH_3$-4
c,Nu = SPh
d,Nu = N-Piperidinyl
e,Nu = $NHNH_2$

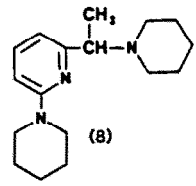
(5)

Most of the substitution reactions in the triazolopyridine series have been done with the 3-methyl-7-bromo derivative (6), because a substituent at position 3 makes for greater stability in the products. Compound (6) reacted with sodium methoxide, ethoxide, or *n*-propoxide in the appropriate alcohol at its boiling point to give the 7-substituted triazolopyridines (7a)-(7c). Sodium phenoxide, sodium 4-methoxyphenoxide, and sodium thiophenoxide, all in DMF at 90-100°C, gave the derivatives (7d)-(7f). Boiling ethanolic solutions of piperidine or of hydrazine converted the bromide (6) into the 7-piperidino derivative (7g) and the 7-triazolopyridyl hydrazine (7h) respectively, in lower (~60%) but acceptable yields. All these 7-substituted triazolopyridines showed in the n.m.r. spectrum an upfield displacement of the double doublet due to H6, which provided an excellent reference signal for quantitative estimation of such derivatives in mixtures (see below). No substitution was achieved from the bromo compound (6) with azide ion, or with potassium isothiocyanate. A second product (15% yield) was isolated from the reaction between bromide (6) and piperidine in ethanol, and became equal in weight to the 7-piperidino derivative (7g) when the reaction was conducted in boiling piperidine. The new product showed the presence of two piperidine residues in different environments; the shifts for the two sets of 4H next to the piperidine nitrogen differed by 1.1 p.p.m. The most interesting feature of the n.m.r. spectrum was the absence of a singlet due to the methyl group on the triazolopyridine ring, and its replacement by a doublet due to the system -CH-CH_3, characteristic of an α-substituted ethyl group attached to a pyridine ring. The presence of signals at δ6.35 and 6.5 (two overlapping doublets) confirmed the presence of a 2-aminopyridine; hence the new compound is the pyridine (8). Further studies of this reaction are reported at the end of the discussion. The parent 7-bromotriazolopyridine (9) reacted with sodium methoxide in methanol to give a crude product, which from the n.m.r. spectrum was mainly 7-methoxytriazolopyridine (10). However, all attempts at purification by chromatography led to decomposition; thus passage across a Chromatotron plate gave several compounds, one of which was shown to be ring opened product (19) (see below). Other nucleophiles gave mixtures of products, and we have yet to solve the problem of clean nucleophilic substitution on triazolopyridines with no stabilizing substituent at C3.


(6)


(9), R = Br
(10), R = OMe

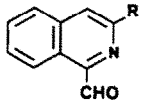

(7) a, Nu = OMe
b, Nu = OEt
c, Nu = OPr^{n}
d, Nu = OPh
e, Nu = $OC_6H_4OCH_3$-4
f, Nu = SPh
g, Nu = N-Piperidinyl
h, Nu = $NHNH_2$

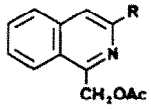

(8)

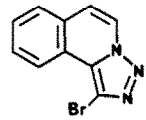
The second phase of the work was to use our ring opening procedures[5] to convert a representative selection of the new triazolo-isoquinolines and -pyridines into isoquinolines and pyridines respectively. Selenium dioxide has been shown to convert most triazolopyridines into acylpyridines,[5] but failed to react with triazoloisoquinoline (2).[4] The destabilizing effect of a substituent *peri* to a nitrogen of the triazole ring clearly assists ring opening reagents and, in contrast to our observation with triazoloisoquinoline (2), the 5-methoxy-, 5-(4-methoxyphenoxy)- and 5-piperidino-triazoloisoquinolines (4a), (4b), and (4d), and the 5-bromo derivative (3), were all cleanly opened by selenium dioxide in boiling xylene to give the isoquinoline-1-carboxaldehydes (11a), (11b), (11d), and (12) respectively. The crude yield of the piperidinoisoquinoline (11d) was excellent, and the material almost pure, but the compound proved unstable to chromatography.

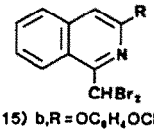
Boiling acetic acid converted compound (4b) into the 1-acetoxymethylisoquinoline (13b) in excellent yields. Bromine failed to open the triazole ring of triazoloisoquinoline (2) even under drastic conditions, giving instead 1-bromotriazoloisoquinoline (14), but the substituted triazoloisoquinolines (4b) and (3) were converted at room temperature into the 1-dibromomethyl-isoquinolines (15b) and (16). Our fourth reagent for opening the triazole rings, hot dilute sulphuric acid, proved unsuitable for these substituted triazoloisoquinolines, giving mixtures which were hard to purify.

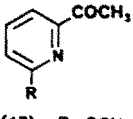
A large amount of information on the opening of triazolopyridine rings is already available.[5] We used selenium dioxide in boiling chlorobenzene to convert compounds (7a) and (7e) into the 2-acetylpyridines (17a) and (17e), and glacial acetic acid to convert compounds (7d) and (7f) into the 2-acetoxyethylpyridines (18d) and (18f). The 7-methoxytriazolopyridine (10) was converted by hot aqueous sulphuric acid into 2-hydroxymethyl-6-methoxypyridine (19). Attempts to purify 7-methoxytriazolopyridine (10) using a silica Chromatotron plate produced substantial amounts of the hydroxymethylpyridine (19).

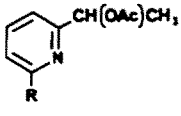

(11) a, R = OMe
b, R = $OC_6H_4OCH_3$-4
d, R = N-Piperidinyl
(12) R = Br

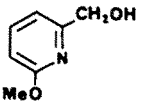

(13) b, R = $OC_6H_4OCH_3$-4
d, R = N-Piperidinyl


(14)


(15) b, R = $OC_6H_4OCH_3$-4
d, R = N-Piperidinyl
(16) R = Br


(17) a, R = OCH_3
e, R = $OC_6H_4OCH_3$-4

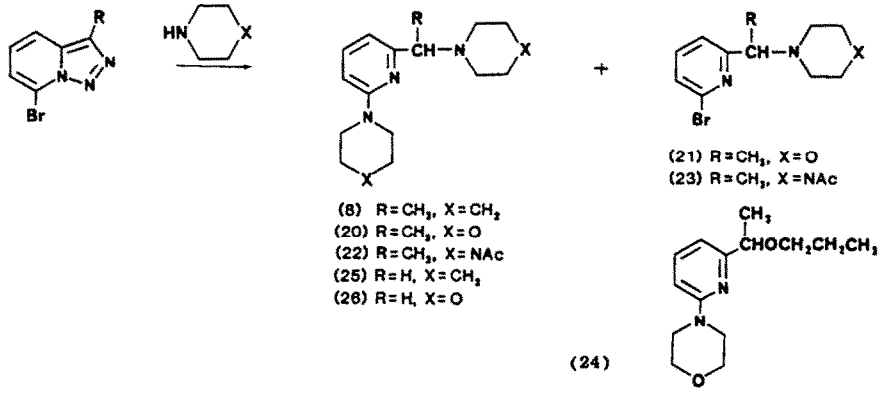

(18) d, R = OC_6H_5
f, R = N-Piperidinyl


(19)

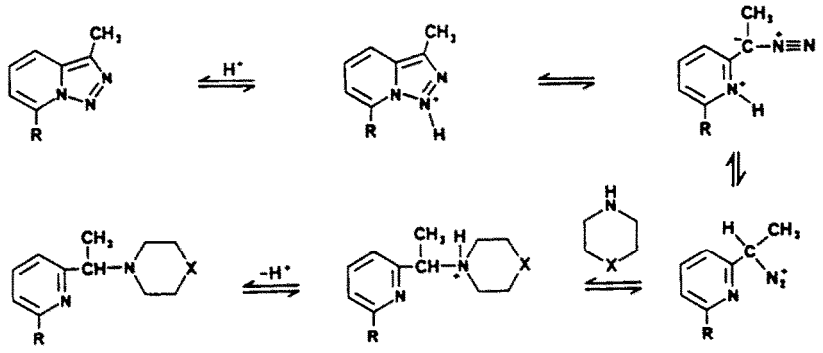
The identification of a pyridine derivative (8) among the products of reaction between the bromo triazolopyridine (6) and piperidine led to a more detailed study of reactions of the bromocompound (6) with secondary amines. When a solution of compound (6) in piperidine was boiled, the crude product was seen from its n.m.r. spectrum to be a 1:1 mixture of 7-piperidinotriazolopyridine (7g) and the pyridine (8); the reaction was approximately 8 times as fast as that using an ethanol solution of piperidine. A solution of morpholine in boiling ethanol slowly converted the bromocompound (6) into two products. The same two products could be obtained more quickly and in better yield, together with a new product, when boiling *n*-propanol was used as the solvent. Chromatography gave a poor return of the two pure products common to both procedures. One (31.6% on unrecovered bromocompound) showed many n.m.r. spectral similarities with the piperidine product (8). Analysis and mass spectrum established the structure as (20). The second product (23%) showed some similarity with compound (20), but had one morpholine substituent, attached to the side chain. The aromatic region of the n.m.r. spectrum lacked the upfield signals characteristic of H3 and H5 in a 2-aminopyridine, and the molecular ion showed the presence of a bromine atom. Analysis confirmed the molecular formula as $C_{11}H_{15}BrN_2O$, and the compound is the 6-bromopyridine (21). The product obtained uniquely from the reaction in boiling *n*-propanol was also a pyridine and, from the n.m.r. spectrum, had a morpholine substituent in the α-position of the pyridine ring. There were two methyl doublets, one at δ0.85-0.95 and the other at δ1.3-1.4, multiplets at δ1.45-1.60 (4H) and δ3.15-3.80 (6H), and a quartet at δ4.05-4.35. Thus the compound is a 2,6-disubstituted pyridine, and the molecular formula, $C_{14}H_{22}N_2O_2$, establishes it as the *n*-propyloxy derivative (24), where the propanol solvent has competed successfully with morpholine in the ring opening step. When N-acetylpiperazine was used as the nucleophile in *n*-propanol as solvent, the bromocompound (6) gave two products, easily identified by their spectra as the pyridines (22) and (23). The recorded yields of these pyridines (8) and (20)-(23) are all lower than the yields estimated by n.m.r. spectroscopy on the crude products, because all were decomposed by chromatography on alumina, florisil, or silica. Thus, compounds (7g) and (8) were obtained in approximately equal yield when the bromo compound (6) was boiled in piperidine; separation by Chromatotron (silica plate) gave recovered compound (8) equivalent to only 20% of recovered compound (7g).

When a solution of 7-bromotriazolopyridine (9) in piperidine was boiled the only product, isolated by distillation in over 90% yield, was the 2,6-disubstituted pyridine (25). Similarly, from 7-bromotriazolopyridine (9) and boiling morpholine the sole isolated product was the 2,6-disubstituted pyridine (26).

We are uncertain of the mechanism of this ring opening reaction. It was found that 3-methyl triazolopyridine is stable to boiling piperidine, with or without piperidine hydrobromide so that the 7-substituent seems necessary. The replacement of the bromine atom at position 7 is not a prerequisite of ring opening, as is shown by the isolation of compounds (21) and (23), but since no other nucleophiles appear to lead to ring opening we conclude that protonation, probably by base hydrobromide, is necessary to initiate the reaction. A mechanism is suggested in the SCHEME although there is no conclusive evidence.



SCHEME



EXPERIMENTAL

M.p.s. were determined on a Kofler hot stage and are uncorrected. In purification by Chromatotron (2 mm plates) and for p.l.c. silica (Merck PF_{254}) was used. Selenium dioxide was sublimed before use. N.m.r. spectra were determined for solutions in $CDCl_3$ unless otherwise stated.

5-Bromotriazoloisoquinoline (3) was prepared from 5-lithiotriazoloisoquinoline and 1,2-dibromo-1,1,2,2-tetrachloroethane (DBTCE) in 65% yield as described.[1]

7-Bromo-3-methyltriazolopyridine (6) was prepared from 7-lithio-3-methyltriazolopyridine and DBTCE in 70-80% yield.[1]

7-Bromotriazolopyridine (9) was similarly prepared in 60-70% yield.[1]

5-Methoxytriazoloisoquinoline (4a). - A solution of sodium (30 mg) in anhydrous methanol (3 ml) was treated with the bromocompound (3) (100 mg) and the solution boiled (20 h). The cooled mixture was poured into water, extracted with dichloromethane, and the dried ($MgSO_4$) organic layer was filtered and evaporated. Purification on a silica plate, eluting with ethyl acetate/hexane (1:2) gave bromocompound (3), (9 mg) and then 5-methoxytriazoloisoquinoline (40 mg, 50% on unrecovered bromide). (Found: C, 66.05; H, 4.25; N, 20.85. $C_{11}H_9N_3O$ requires C, 66.35; H, 4.5; N, 21.1%). δ4.15 (3H, s), 6.25 (1H, s, H6), 7.2-7.6 (3H, m), 7.7-8.0 (1H, m), 8.25 (1H, s, H1).

5-(4-Methoxyphenoxy)triazoloisoquinoline (4b). - A solution of 4-methoxyphenol (0.79 g) and sodium hydroxide (0.3 g) in anhydrous DMF (15 ml) was heated to boiling (30 min) to form the salt. Addition of the bromide (3) (1 g) was followed by further boiling (20 h). Concentration, in vacuo, treatment of the residue with 5% sodium hydroxide and dichloromethane, drying of the combined organic extracts, filtration, and evaporation gave almost pure 5-(4-methoxyphenoxy)-triazoloisoquinoline (4b) m.p. 151.8-153.8°C (from isopropanol), (0.79 g, 86%). (Found: C, 70.6; H, 4.5; N, 14.25. $C_{17}H_{13}N_3O_2$ requires C, 70.1; H, 4.45; N, 14.45%). δ3.8 (3H, s), 6.15 (1H, s, H6), 6.85 (2H, d, J=9 Hz), 7.15 (2H, d, H=9 Hz), 7.3-7.5 (3H, m), 7.8-8.1 (1H, m), 8.35 (1H, s, H1).

5-Phenylthiotriazoloisoquinoline (4c). - Prepared as described for (4b), but using thiophenol. The crude product was purified by p.l.c. (eluent ethylacetate/hexane, 1:3) to give 5-phenylthiotriazoloisoquinoline (4c), m.p. 178-179°C (cyclohexane) (15% yield). (Found: C, 69.3; H, 3.85; N, 14.9. $C_{16}H_{11}N_3S$ requires C, 69.3; H, 3.95; N, 15.15%). δ6.6 (1H, s, H6), 7.3-7.7 (8H, m), 7.9-8.1 (1H, m), 8.35 (1H, s, H1).

5-(N-Piperidinyl)triazoloisoquinoline (4d). - A solution of bromotriazoloisoquinoline (3) (1 g.) in piperidine (25 ml) was boiled (20 h). A precipitate formed and was filtered from the cooled solution. The precipitate was dissolved in water and the aqueous layer extracted with dichloromethane. The original filtrate and the organic extracts were dried (Na_2SO_4) and evaporated to give 5-piperidinyltriazoloisoquinoline (4d), m.p. 205-206°C (acetone) (1 g, almost

quantitative). (Found: C, 71.6; H, 6.45; N, 22.0. $C_{15}H_{16}N_4$ requires C, 71.4; H, 6.35; N, 22.2%). δ1.8 (6H, m), 3.3-3.4 (4H, m), 6.4 (1H, s, H6). 7.4-7.6 (3H, m), 7.85-8.1 (1H, m), 8.32 (1H, s, H1).

N-(Triazoloisoquinoline-5-yl)hydrazine (4e). - A solution of bromocompound (3) (0.55 g) in hydrazine hydrate (80%, 15 ml) was heated at 90-100°C (52 h). Excess hydrazine was evaporated under reduced pressure. The residue was treated with saturated aqueous $NaHCO_3$, extracted with dichloromethane, and the organic layers dried (Na_2SO_4) and evaporated. Crude material was purified on a Chromatotron, eluting with hexane containing increasing amounts of ethyl acetate, to give triazoloisoquinolinyl hydrazine (0.365 g, 83%), characterized as the acetone hydrazone (5), m.p. 161-163°C (cyclohexane). (Found: C, 64.85; H, 5.15; N, 22.3 $C_{13}H_{13}N_5$ requires C, 65.25; H, 5.45; N, 29.3%). δ2.05 (3H, s), 2.15 (3H, s), 6.8 (1H, s, H6), 7.2-7.65 (3H, m), 7.8-7.95 (1H, m), 8.4 (1H, s, H1).

Substitution Reactions on 7-Bromotriazolopyridines.

General Procedures: The bromotriazolopyridine (3) or (9) (10 mmol) was added to a solution of the nucleophile in a suitable solvent. Conditions, yields, and m.p. are given for each compound; microanalytical and n.m.r. data are gathered in Tables 1 and 2. Sodium salts of the oxygen or sulphur nucleophiles were prepared using sodium hydride. Solvents were evaporated under reduced pressure, the residues treated with dilute sodium hydroxide (for phenols or thiophenols), or with saturated sodium bicarbonate, and organic materials extracted by dichloromethane. Crude products were crystallized, or purified on Chromatotron plates, eluting with mixtures of ethyl acetate and petroleum (b.p. 60-80°C).

7-Methoxy-3-methyltriazolopyridine (7a). - Made from bromide (6) and sodium methoxide in boiling methanol (24 h) in 90% yield, m.p. 101-102°C (from cyclohexane).

7-Ethoxy-3-methyltriazolopyridine (7b). From bromide (6) and sodium ethoxide in boiling ethanol (18 h), in 51% yield, m.p. 88-89°C (from cyclohexane).

3-Methyl-7-(*n*-propoxy)triazolopyridine (7c). - From bromide (6) and sodium *n*-propoxide in boiling *n*-propanol (18 h) in 37% yield, b.p. 139°C/0.1 mm Hg.

3-Methyl-7-phenoxytriazolopyridine (7d). - From bromide (6) and sodium phenoxide in DMF at 95°C (72 h) in 60% yield, m.p. 76-76.5°C (from petroleum, b.p. 60-80°C).

7-Anisyloxy-3-methyltriazolopyridine (7e). - From bromide (6) and sodium *p*-methoxyphenoxide in DMF at 95°C (15 h) in 90% yield, m.p. 128-128.5°C (from carbon tetrachloride).

3-Methyl-7-phenylthiotriazolopyridine (7f). - From bromide (6) and sodium thiophenoxide in DMF at 95°C (17 h) in 95% yield, m.p. 118-119°C (from carbon tetrachloride).

3-Methyl-7-(N-piperidinyl)triazolopyridine (7g). - From bromide (6) and piperidine in boiling ethanol (71 h) or from bromide (6) in boiling piperidine (24 h). Yields were 65% or 50%, and the compound had m.p. 101-103°C (from cyclohexane). Varying quantities of compound (8) were also obtained.

3-Methyltriazolopyridin-7-ylhydrazine (7h). - From bromide (6) and hydrazine hydrate in boiling ethanol (100 h) in 65% yield, m.p. 154-155°C (from ethyl acetate).

7-Methoxytriazolopyridine (10). - From bromide (9) and sodium methoxide in boiling methanol (24 h) in 95% yield. Unstable to chromatography or recrystallization.

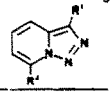


Table 1. Analytical Data for New 7-Substituted Triazolopyridines

	R^1	R^2	FOUND C	FOUND H	FOUND N	FORMULA	REQUIRED C	REQUIRED H	REQUIRED N
(7a)	CH_3	OCH_3	59.0	5.2	25.75	$C_8H_9N_3O$	58.9	5.55	25.75
(7b)	CH_3	OC_2H_5	61.05	6.3	24.0	$C_9H_{11}N_3O$	61.0	6.2	23.7
(7c)	CH_3	OC_3H_7-n	62.75	6.65	21.75	$C_{10}H_{13}N_3O$	62.8	6.8	22.0
(7d)	CH_3	OC_6H_5	69.0	4.85	18.6	$C_{13}H_{11}N_3O$	69.3	4.9	18.65
(7e)	CH_3	$OC_6H_4OCH_3$-4	65.65	5.05	16.55	$C_{14}H_{13}N_3O_2$	65.85	5.15	16.45
(7f)	CH_3	SC_6H_5	64.95	4.55	17.7	$C_{13}H_{11}N_3S$	64.7	4.6	17.4
(7g)	CH_3		66.7	7.75	26.0	$C_{12}H_{16}N_4$	66.6	7.5	25.9
(7h)	CH_3	$NHNH_2$	51.2	5.15	43.0	$C_7H_9N_5$	51.5	5.5	42.9
(10)	H	OCH_3	unstable						

Table 2. N.m.r. data (^{1}H) of 7-Substituted Triazolopyridines 

			δ Values (ppm)					J Values (Hz)
	R^1	R^2	H3	H4	H5	H6	Other	
(7a)	CH_3	OCH_3	2.5(CH_3)	<7.0 -	7.2(m)>	6.0-6.2(dd)	4.1(3H s,OCH_3)	$J_{4,6}$=3, $J_{5,6}$=6
(7b)	CH_3	OCH_2CH_3	2.6 (CH_3)	<7.0 -	7.2(m)>	6.0-6.2(dd)	1.45-1.6 (3H,t,CH_3) 4.3-4.7 (2H,q,OCH_2)	$J_{4,6}$=3, $J_{5,6}$=6
(7c)	CH_3	$OCH_2CH_2CH_3$	2.6 (CH_3)	<7.0 -	7.2(m)>	6.1-6.3(dd)	0.9-1.3 (3H,t,CH_3) 1.6-2.3 (2H,m) 4.0-4.3 (2H,q,OCH_2)	$J_{4,6}$=3 $J_{5,6}$=6
(7d)	CH_3	OC_6H_5	2.55(CH_3)	<6.8 -	7.3(m)>	5.95-6.1(dd)	6.8-7.3 (5H,m,C_6H_5)	$J_{4,6}$=1, $J_{5,6}$=6.5
(7e)	CH_3	$OC_6H_4OCH_3$-4	2.66(CH_3)	<6.9 -	7.1(m)>	5.95-6.1(dd)	3.84(3H,s, OCH_3), 7.0-7.1 (2H,d,H2',6'), 7.14-7.24 (2H,d,H3',5')	$J_{4,6}$=1 $J_{5,6}$=7 $J_{2',3'}$=10
(7f)	CH_3	SC_6H_5	2.64 (CH_3)	7.38-7.52(m)	6.9-7.1(dd)	6.25-6.34(dd)	7.38-7.52(3H,m) 7.6-7.7(2H,m)	$J_{4,5}$=8.8, $J_{4,6}$=1, $J_{5,6}$=7
(7g)	CH_3		2.6(CH_3)	<7.2 -	7.5(m)>	6.18-6.26(dd)	1.5-1.9(6H,m) 3.35-3.5(4H,m)	$J_{4,6}$=2, $J_{5,6}$=6.3
(7h)	CH_3	$NHNH_2$	2.6(CH_3)	7.07-7.1(dd)	7.2-7.4(m)	6.44-6.5(dd)	3.94(3H, brs,$NHNH_2$)	$J_{4,5}$=8.7, $J_{4,6}$=1.3, $J_{5,6}$=7
(10)	H	OCH_3	7.8(s)	<6.8 -	7.3(m)>	6.0-6.2(dd)	3.95(3H, s,OCH_3)	$J_{4,6}$=2, $J_{5,6}$=7

Ring Opening Reactions on Triazolo-isoquinolines or -pyridines. - The procedures have been previously described.[5] Conditions, yields, and m.p. or b.p. are given for each compound. Analytical data for new pyridines is given in Table 5 and the n.m.r. data is given in Table 3 for isoquinolines and in Table 4 for pyridines.

3-Methoxyisoquinoline-1-carboxaldehyde (11a). - From compound (4a) and selenium dioxide in boiling xylene (1 h), in 85% yield, m.p. 79-81°C (lit.[7] m.p. 86-87°C).

3-Anisyloxyisoquinoline-1-carboxaldehyde (11b). - From compound (4b) and selenium dioxide in boiling xylene (12 h) in 88% yield, m.p. 84.5-86°C (from petroleum, b.p. 40-60°C). (Found: C, 73.3; H, 4.8; N, 4.9. $C_{17}H_{13}NO_3$ requires C, 73.1; H, 4.65; N, 5.0%).

3-(N-Piperidinyl)isoquinoline-1-carboxaldehyde (11d). - From compound (4d) and selenium dioxide in boiling xylene (10 h), in 82% crude yield. The compound proved unstable to chromatography. N.m.r. data in Table 3.

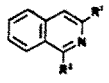
3-Bromoisoquinoline-1-carboxaldehyde (12). - From compound (3) and selenium dioxide in boiling xylene (10 h) in 85% yield, m.p. 119-120°C (from petroleum, b.p. 40-60°C). (Found: C, 51.0; H, 2.4; N, 5.7. $C_{10}H_6BrNO$ requires C, 50.9; H, 2.55; N, 5.95%).

1-Acetoxymethyl-3-anisyloxyisoquinoline (13b). - From compound (4b) in boiling acetic acid (2.3 h) in 91% yield, m.p. 80.6-82.2°C (from hexane). (Found: C, 70.5; H, 5.2; N, 4.45. $C_{19}H_{17}NO_4$ requires C, 70.55; H, 5.25; N, 4.35%).

3-Anisyloxy-1-dibromomethylisoquinoline (15b). - From compound (4b) and bromine in dichloromethane at room temperature (2 h) in 57% yield, m.p. 75.5-77.5°C (from petroleum, b.p. 40-60°C). (Found: C, 48.15; H, 2.95; N, 3.35. $C_{17}H_{13}Br_2NO_2$ requires C, 48.2; H, 3.05; N, 3.78%).

3-Bromo-1-dibromomethylisoquinoline (16). - From compound (3) and bromine in dichloromethane at room temperature (1 h) in 85% yield, m.p. 136-138°C (lit.[1] m.p. 136-138°C).

Table 3. N.m.r. Data of 1,3-Disubstituted isoquinolines



	R^1	R^2	Shifts in δ H4	H5	H6/H7	H8	OTHER	J values (Hz)
(11a)	OCH_3	CHO	7.25(s)	<7.4 -	7.85(m)>	9.05-9.3(m)	10.4(1H,s,CHO), 4.05(3H,s,OCH_3)	
(11b)	Anisyloxy	CHO	7.15(s)	<7.25 -	7.65(m)>	8.9-9.15(m)	10.1(1H,s,CHO), 7.1(2H,d), 6.85(2H,d), 3.8(3H,s,OCH_3)	$J_{2',3'}$=9
(11d)		CHO	6.6(s)	<6.85 -	7.3(m) >	8.85-8.87(m)	10.0(1H,s,CHO), 1.6(6H,m), 3.55(4H,m)	
(12)	Br	CHO	7.9(s)	<7.7 -	7.9(m) >	5.9-9.2(m)	10.1(1H,s,CHO)	
(13b)	Anisyloxy	CH_2OCOCH_3	6.9(s)	7.05-7.45(m)	<7.45-7.65(m)>	7.95(dd)	2.05(3H,s,CH_3CO), 3.8(3H,s,OCH_3), 5.6(2H,s,CH_2O), 6.7-7.05(5H,m)	$J_{7,8}$=9, $J_{6,8}$=1
(13d)		CH_2OCOCH_3	6.62(s)	7.35(dd)	<6.9-7.25(m)>	7.75(dd)	1.7(6H,m), 2.12(2H,s,CH_3CO), 3.55(4H,m), 5.55(2H,s,CH_2O).	$J_{7,8}$=8, $J_{6,8}$=1, $J_{5,6}$=8, $J_{5,7}$=1.
(15b)	Anisyloxy	$CHBr_2$	7.4(s)	<6.7 -	7.6(m) >	8.4(dd)	3.8(3H,s,OCH_3), 6.6-7.1(4H d of d), H2',6' and H3',5')	
(15d)		$CHBr_2$	6.6(s)	7.7-8.4(m)	<7.1-7.6(m) >	7.7-8.4(m)	7.6(6H,m), 3.2(4H,m), 7.0(1H,s,$CHBr_2$).	
(16)	Br	$CHBr_2$	7.8(s)	<7.5 -	7.7(m) >	8.5-8.8(m)	7.0(1H,s,$CHBr_2$)	

2-Acetyl-6-methoxypyridine (17a). - From compound (7a) and selenium dioxide in boiling chlorobenzene (1 h), in 60% yield m.p. 40-41°C (sublimed).

2-Acetyl-6-anisyloxypyridine (17e). - From compound (7e) and selenium dioxide in boiling chlorobenzene (1 h), in 70% yield, m.p. 75-76°C (from petroleum, b.p. 60-80°C).

α-(6-Phenoxy-2-pyridine)ethyl Acetate (18d). - From compound (7d) in boiling acetic acid (2.5 h), in 80% yield, b.p. 130°/0.1 mm Hg (bulb tube).

α-(6-N-piperidinyl-2-pyridine)ethyl Acetate (18f). - From compound (7f) in boiling acetic acid (2 h), in 75% yield, b.p. 135°/0.05 mm Hg (bulb tube).

6-Methoxy-2-pyridinemethanol (19). - From compound (10) in 2N sulphuric acid at 95°C (2 h), in 80% yield, b.p. 70°C/0.1 mm Hg (bulb tube). (lit.[8] b.p. 72-73°C/0.06 mm Hg).

2-(1-N-Piperidinylethyl)-6-(N-piperidinyl)pyridine (8). - From bromide (6) and piperidine in boiling ethanol (72 h) or boiling piperidine (24 h) in 15% and 50% yields respectively, b.p. 140-145°C/0.05 mm Hg. For analysis a dipicrate was prepared, m.p. 185-187°C (from ethanol).

2-(1-(N-Morpholinyl)ethyl)-6-(N-morpholinyl)pyridine (20), 2-(1-N-Morpholinyl)ethyl-6-bromopyridine (21), and 2-(1-n-Propyloxy)ethyl-6-(N-Morpholinyl)pyridine (24). - From bromide (6) and morpholine in boiling ethanol (168 h) compounds (20) and (21) were obtained in yields of 20% and 10%. Compound (20) had b.p. 125°C/0.05 mm Hg, and compound (21) had b.p. 120°C/0.025 mm Hg (both in bulb tubes). From bromide (6) and morpholine in boiling n-propanol (97 h), compounds (20), (21), and (24) were obtained in yield of 50%, 28%, and 13% respectively. Compound (24) had b.p. 140°C/0.06 mm Hg (bulb tube). From bromide (6) in boiling morpholine compound (20) was obtained in 58% yield.

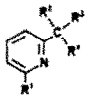
2-(α-(4-Acetylpiperazin-1-yl)ethyl-6-(4-acetylpiperazin-1-yl)pyridine (22) and 6-Bromo-2-(α-(4-acetylpiperazin-1-yl)ethyl pyridine (23). - From bromide (6) and N-acetylpiperazine in boiling n-propanol (48 h) compounds (22) and (23) were obtained in yields of 22% and 34%

respectively. Compound (23) was distilled, b.p. 180°C/0.05 mm Hg, but compound (22) could not be distilled without decomposition.

6-(N-Piperidinyl)-2-(N-piperidinylmethyl)pyridine (25). - From bromide (9) in boiling piperidine (16 h), in 90% yield, b.p. 150°C/0.05 mm Hg (bulb tube). For analysis a dipicrate was prepared m.p. 146-148°C (from ethanol).

6-(N-Morpholinyl)-2-(N-Morpholinylmethyl)pyridine (26). - From bromide (9) in boiling morpholine (16 h), in 90% yield, m.p. 72-73°C (from petroleum, b.p. 60-80°C).

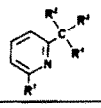
Table 4. N.m.r. Data (^{1}H) on 2,6-Disubstituted Pyridines in $CDCl_3$



	R^1	R^2	R^3	Shifts in δ (p.p.m.) R^4	H3	H4	H5	Other	J Values Hz
(17a)	OCH_3	<	0 >	CH_3	<7.6	7.8(m)	6.85-7.0(dd)	2.68(3H,s,CH_3CO), 4.0(3H,s,OCH_3)	$J_{3,4}$-, $J_{4,5}$=7
(17e)	Ar	<	0 >	CH_3	<7.7	7.85(m)	6.8-7.1(m)	2.5(3H,s,CH_3CO), 3.84(3H,s,OCH_3), 6.88-6.97(2H,d), 7.08-7.19(2H,d)	$J_{2',3'}$=9
(18d)	OC_6H_5	H	OCO_{C3}	CH_3	[a]	7.4-7.7(t)	6.55-6.7(d)	1.45-1.55(3H,d, CH_3CH), 2.0(3H, s,CH_3CO_2), 5.5-5.9 1H,q,$CHCH_3$)6.8-7.4 (6H,m,Ph+H3)	$J_{4,5}$=9, J_{CH,CH_3}=7
(18f)		H	$OCOCH_3$	CH_3	6.4-6.5(d)	7.2-7.5(dd)	6.45-6.55(d)	1.4-1.7(9H,m), 2.1(3H,s,CH_3CO), 3.3-3.7(4H,m)	$J_{3,4}$-, $J_{4,5}$=8 J_{CH,CH_3}=7
(19)	OCH_3	H	OH	H	6.75-6.9(d)	7.4-7.7(t)	6.55-6.7(d)	3.3-3.7(1H,brs,OH), 4.0(3H,s,OCH_3), 4.7(2H,s,CH_2OH)	$J_{3,4}$-, $J_{4,5}$=7
(8)		H		CH_3	6.35-6.7(d)	7.1-7.5(t)	6.3-6.45(d)	1.25-1.4(3H,d, CH_3CH),1.4-1.8 (12H,m),2.2-2.7 (4H,m),3.1-3.7 (5H,m)	$J_{3,4}$=7, $J_{4,5}$=8
(20)		H		CH_3	6.55-6.7(d)	7.22-7.5(t)	6.3-6.43(d)	1.2-1.3(3H,d, CH_3CH), 2.1-2.5 (4H,m),3.1-3.8 (13H,m)	$J_{3,4}$=7, $J_{4,5}$=8
(21)	Br	H		CH_3	<----------	7.1-7.6	---------->	1.15-1.3(3H,d, CH_3CH),2.1-2.7 (4H,m),3.2-3.7 (5H,m).	
(24)		H	OPr^n	CH_3	6.7-6.8(d)	7.3-7.6(t)	6.4-6.5(d)	0.8-1.1(3H,t, CH_3CH_2),1.3-1.4 (3H,d,CH_3Ch),1.3-1.9(2H,m),3.2-3.45 (2H,t,OCH_2CH_2), 3.35-3.7(4H,m, CH_2N),3.7-4.0(3H,m, CH_2O),4.1-4.5 (1H,q,$CHCH_3$).	$J_{3,4}$-, $J_{4,5}$=7
(23)	Br	H		CH_3	<----------	7.1-7.7(m)	---------->	1.3-1.3(3H,d, CH_3CH),2.0(3H,s). 2.3-2.6(4H,m), 3.3-3.7(5H,m).	
(25)		H		H	6.6-6.7(d)	7.2-7.5(t)	6.35-6.5(d)	1.1-1.9(12H,m), 2.3-2.6(4H,m), 3.2-3.8(6H,m).	$J_{3,4}$=7 $J_{4,5}$=8
(26)		H		H	6.6-6.8(d)	7.2-7.6(t)	6.25-6.55(d)	2.2-2.6(4H,m) 3.2-3.9(14H,m, including CH_2 singlet at 3.45)	$J_{3,4}$=7. $J_{4,5}$=8

[a] Under 6H multiplet, δ6.8-7.4
Ar = $OC_6H_4OCH_3$-4

Table 5. Analytical Data for New Disubstituted Pyridines



	R^1	R^2	R^3	R^4	FOUND C	FOUND H	FOUND N	FORMULA	REQUIRED C	REQUIRED H	REQUIRED N
(17a)	OCH_3	<	O	>	CH_3	63.35	5.95	9.25	$C_8H_9NO_2$	63.55	6.0	9.25
(17e)	OAr^a	<	O	>	CH_3	68.85	5.4	5.5	$C_{14}H_{13}NO_3$	69.15	5.4	5.75
(18d)	OPh	H	OAc		CH_3	69.8	5.95	5.5	$C_{15}H_{15}NO_3$	70.0	5.95	5.45
(18f)		H	OAc		CH_3	66.45	8.2	11.0	$C_{14}H_{20}N_2O_2$	66.5	8.55	11.1
(8)		H			CH_3	47.6	4.55	17.25	$C_{29}H_{33}N_9O_{14}$[b]	47.3	4.6	17.0
(20)		H			CH_3	65.0	8.05	15.05	$C_{15}H_{23}N_3O_2$	65.0	8.3	15.15
(21)	Br	H			CH_3	48.75	5.75	10.45	$C_{11}H_{15}BrNO$	48.7	5.6	10.35
(24)		H	OPr^n		CH_3	67.4	8.5	11.4	$C_{14}H_{22}N_2O_2$	67.15	8.85	11.2
(23)	Br	H			CH_3	-	-	13.72	$C_{13}H_{18}BrN_3O$[c]	-	-	13.45
(25)		H			H	74.3 46.55	10.1 4.1	16.45 17.5	$C_{16}H_{25}N_3$ $C_{28}H_{31}N_9O_{14}$[b]	74.1 46.85	9.7 4.35	16.2 17.55
(26)		H			H	64.05	8.3	16.1	$C_{14}H_{21}N_3O_2$	63.85	8.05	15.95

[a] Ar = 4-$CH_3OC_6H_4$ [b] Dipicrate [c] M^+ 311,313

References

1. Part 7. B. Abarca, R. Ballesteros, F. Mojarred, G. Jones, and D.J. Mouat, J. Chem. Soc., Perkin Trans. I, 1987, 1865.
2. G. Jones and D.R. Sliskovic, J. Chem. Soc., Perkin Trans. I, 1982, 967.
3. B. Abarca, D.J. Hayles, G. Jones, and D.R. Sliskovic, J. Chem. Res. (S) 1983, 144; (M), 1983, 1341.
4. B. Abarca, R. Ballesteros, E. Gomez-Alderavi, and G. Jones, J. Chem. Soc., Perkin Trans. I, 1985, 1897.
5. G. Jones, D.J. Mouat, and D.J. Tonkinson, J. Chem. Soc., Perkin Trans. I, 1985, 2719.
6. Preliminary Communication. B. Abarca, R. Ballesteros, G. Jones, and F. Mojarred, Tetrahedron Letters, 1986, 27, 3543.
7. K.J. Gibson, M. d'Alarcao, and N.J. Leonard, J. Org. Chem., 1985, 50, 2462.
8. G.E. Schulz and S. Fedders, Arch. Pharm., 1977, 310, 128.

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