Triazolopyridines. Part 5. The Reactions of 1,2,3-Triazolo[5,1-*a*]isoquinoline: A New Route to 1,3-Disubstituted Isoquinolines

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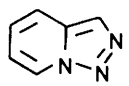
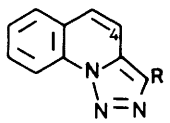
Substitution of 1,2,3-triazolo[1,5-*a*]isoquinoline by electrophiles occurs at position 1, lithiation at position 5. The lithio derivative (**8**) reacts with electrophiles to give 5-substituted derivatives (**9**)—(**13**). Hydrolytic ring opening of compound (**4**) and of compound (**9**) occurs with loss of nitrogen, thus providing a synthesis of 1,3-disubstituted isoquinolines. The conversion of a 3,4-disubstituted triazoloquinoline into a 2,3-disubstituted derivative of quinoline is described. A direct synthesis of *N,N*-dialkylquinolyl- (**21**) and *N,N*-dialkylisoquinolyl-acetamides (**24**) and (**25**) and the conversion of compound (**21**) into *N,N*-diethyltriazoloquinoline-4-carboxamide (**3**) has been achieved.

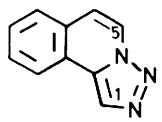
We have shown that triazolopyridine (**1**) undergoes directed lithiation at position 7, thus providing, after reaction with electrophiles and ring opening, a synthesis of 2,6-disubstituted pyridines.[1-3] We have also studied lithiation of the triazoloquinolines (**2**) and (**3**),[4] but were unable to open the five-membered ring of the 4-substituted derivatives of compound (**3**) thus obtained. We now report a study of the reactions of 1,2,3-triazolo[5,1-*a*]isoquinoline (**4**), and show that it can provide a route to 3-substituted 1-isoquinolyl methanols. We have also achieved the conversion of a 4-substituted derivative of the triazoloquinoline (**3**) into a derivative of a 2,3-disubstituted quinoline.



(**1**)

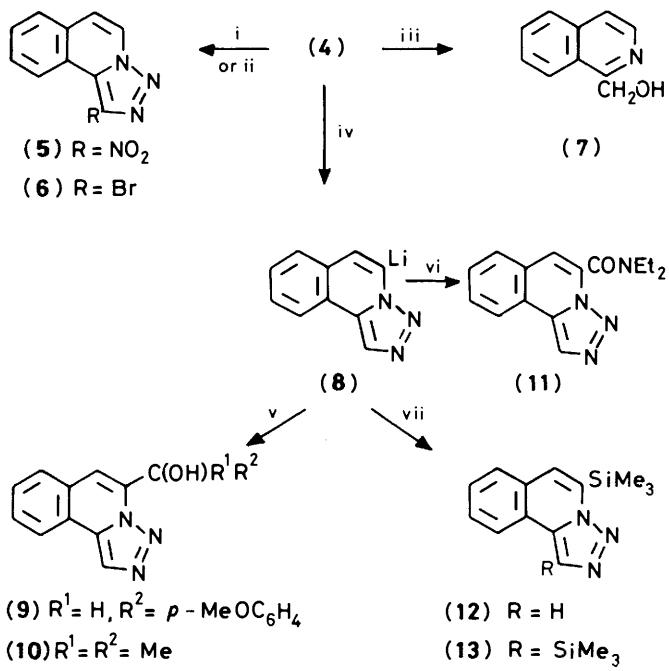


(**2**) R = H
(**3**) R = $CONEt_2$



(**4**)

We obtained our triazoloisoquinoline (**4**) from 1-methylisoquinoline by the direct procedure of Abramovitch and Takaya[5] although our best yields were of the order of 35%. Commercial samples of 1-methylisoquinoline are available at a very high price, but the compound can be synthesized in quantity by a modified Pictet-Gams procedure[6] from ω-aminoacetophenone, or in smaller quantities from isoquinoline using methylsulphoxonium methylide.[7] We first examined direct electrophilic substitution of triazoloisoquinoline (**4**), when attack occurred at position 1. Nitration gave the 1-nitrotriazoloisoquinoline (**5**), and bromination (at low temperature or at 70 °C) gave the 1-bromotriazoloisoquinoline (**6**). The latter reaction was both noteworthy and disappointing; both the triazolopyridine (**1**)[2] and the triazoloquinoline (**2**)[4] are cleanly converted by bromine into 2-dibromomethyl-pyridine[2] and -quinoline,[4] respectively, and in the former case this reaction was important in our synthesis of 2,6-disubstituted pyridines. The position of substitution was clearly shown by the absence of a singlet in the ^1H n.m.r. spectrum at δ 8.3 characteristic of 1-H in compound (**4**). However, treatment of triazoloisoquinoline (**4**) with hot aqueous sulphuric acid gave 1-hydroxymethylisoquinoline (**7**) in 64% yield, so that a route from substituted triazoloisoquinolines to isoquinolines is available.



(**5**) R = NO_2
(**6**) R = Br
(**7**)
(**8**)
(**9**) R^1 = H, R^2 = *p*-$MeOC_6H_4$
(**10**) R^1 = R^2 = Me
(**11**)
(**12**) R = H
(**13**) R = $SiMe_3$

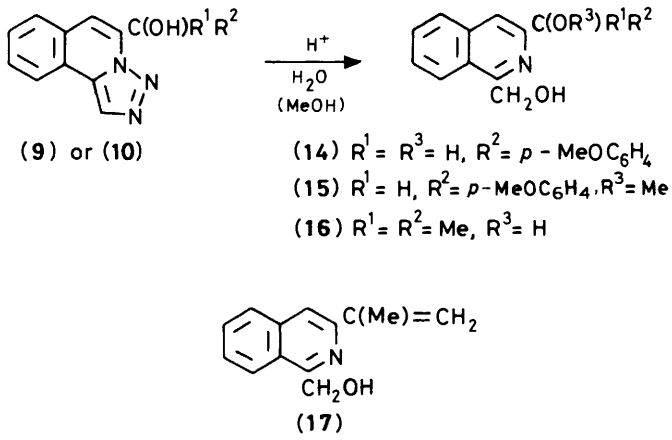
Scheme 1. *Reagents:* i, HNO_3, Ac_2O; ii, Br_2, CCl_4; iii, H_2SO_4, H_2O, 95 °C; iv, Pr^i_2NLi, −40 °C; v, R^1COR^2; vi, Et_2NCOCl; vii, Me_3SiCl

Treatment of an ethereal solution of triazoloisoquinoline at −40 °C with lithium di-isopropylamide gave, after an hour, a lithium derivative. Addition of deuterium oxide and isolation of the triazoloisoquinoline gave a specimen showing only two changes in the ^1H n.m.r. spectrum from the original compound (**4**). The prominent doublet at δ 8.4 due to 5-H had disappeared, and the doublet at δ 7.1 (6-H) had simplifed to a singlet. Thus the lithium derivative must have structure (**8**), and lithiation follows the pattern of triazolopyridine (**1**) rather than triazoloquinoline (**2**). The lithiated derivative (**8**) reacted with anisaldehyde to give the alcohol (**9**) and with acetone to give the alcohol (**10**). Neither showed a n.m.r. signal for 5-H, and both showed a singlet for 6-H. Reaction of the lithium derivative (**8**) with *N,N*-diethylcarbamoyl chloride gave the amide (**11**). The most interesting result was obtained by using trimethylsilyl chloride as co-reagent. Two products were formed, the major (60%) being the 5-trimethylsilyltriazoloisoquinoline (**12**). The

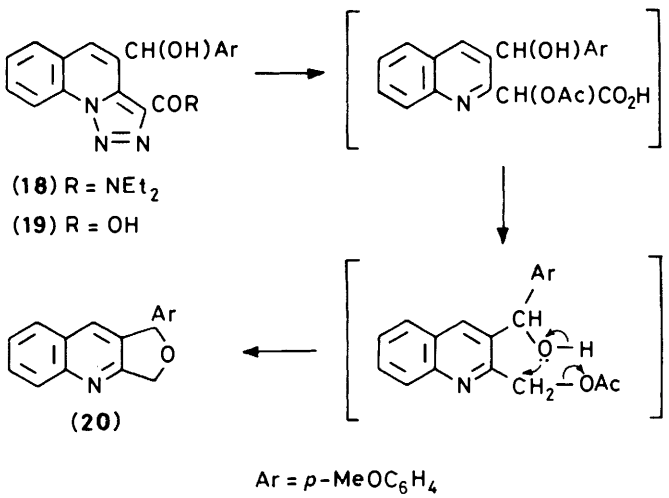
second product (23%), from its elemental analysis and ^{1}H n.m.r. spectrum, was a bis(trimethylsylyl) derivative; the absence of a singlet at δ 8.4 and of the doublet at δ 8.3 showed it to be the 1,5-disubstituted triazoloisoquinoline (**13**). The possibility that the triazoloisoquinoline (**4**) was sufficiently nucleophilic at position 1 to react directly with trimethylsilyl chloride was excluded by the absence of substitution when triazoloisoquinoline (**4**) was stirred for 24 h with trimethylsilyl chloride and *N*-methylpiperidine. It seems probable therefore that a percentage of dianion is formed when triazoloisoquinoline is lithiated, although we detected no measurable incorporation of deuterium when the lithiated triazoloisoquinoline was treated with deuterium oxide.

With the possibility of substitution of triazoloisoquinoline (**4**) at position 5 firmly established, we sought to complete the synthesis of 1,3-disubstituted isoquinolines by discovering a reagent which would open the five-membered ring with loss of nitrogen. Our previously preferred route (bromination, with subsequent hydrolysis of the dibromomethyl derivative[1–4]) failed. Selenium dioxide oxidation, which successfully converts triazolo-pyridines and -quinolines into pyridine and quinoline aldehydes, failed to react with triazoloisoquinoline under a variety of conditions. We were finally successful with hot aqueous sulphuric acid which converted compound (**4**) into isoquinoline-1-methanol (**7**). The less soluble alcohol (**9**) was heated in aqueous sulphuric acid with added methanol, and gave a mixture of two products. The major product was shown by analysis to have the formula $C_{18}H_{17}NO_3$, and by ^{1}H n.m.r. spectroscopy to contain one methoxy group, two hydroxy groups, a singlet methylene signal at δ 5.0, and a singlet methine signal at δ 5.9. The rest of the spectrum clearly indicated the change from triazoloisoquinoline to isoquinoline, by the absence in the new compound of the downfield deshielded multiplet [10-H in compound (**4**)] and of the singlet due to 3-H in compound (**4**). Thus the major product of the hydrolysis was the 1,3-disubstituted isoquinoline (**14**). The analysis of the second product showed a formula $C_{19}H_{19}NO_3$ and the ^{1}H n.m.r. spectrum was very similar to that of compound (**14**) but with an additional methoxy group. The only doubt concerned the site of this methoxy group, and a comparison of the shifts of the methylene and of the methine groups in the minor product with those of compound (**14**) showed a considerable downfield shift only in the methine signal. Hence the minor product of hydrolysis is the 3-(α,4-dimethoxybenzyl) derivative (**15**). We have observed elsewhere[8] the easy conversion of such benzylic alcohols into methyl ethers in acidic aqueous methanol. The combined yields of 1,3-disubstituted isoquinolines was 75%. Thus the entire sequence constitutes a practical formal conversion of 1-methylisoquinoline into a 3-substituted 1-isoquinolylmethanol. The hydrolysis procedure was less successful with the tertiary alcohol (**10**). Again, two products were formed, characterized spectroscopically as the diol (**16**) and the isopropenyl derivative (**17**), but satisfactory analyses were not obtained. The obvious problem of dehydration of tertiary aliphatic alcohols suggests a slight limitation on the substituents which can be introduced into the 3-position of 1-methylisoquinoline by our procedure.

A major disappointment in our study of triazoloquinoline (**2**)[4] was our inability to devise a procedure for the conversion of the disubstituted triazoloquinolines such as compound (**18**) into 2,3-disubstituted quinolines. Subsequently, more detailed study of ring-opening reactions of triazolopyridine (**1**)[8] led us to consider the use of glacial acetic acid. The triazoloquinoline (**18**) could be hydrolysed in high yield to the corresponding acid (**19**), and when a solution of the acid (**19**) in glacial acetic acid was boiled for a prolonged period a single product was obtained of molecular formula $C_{18}H_{15}NO_2$. The ^{1}H n.m.r. spectrum showed the presence of a quinoline nucleus and of a methoxy-



phenyl group. A singlet at δ 8.1 indicated a free γ position, and the only other signals were a singlet at δ 6.27 (1-H) and a pair of doublets (*J* 12 Hz) at δ 5.25 and 5.35. These data are in agreement with the formulation of the hydrolysis product as the dihydrofuro[3,4-*b*]quinoline (**20**). Since this compound is formally a 2,3-disubstituted quinoline, we have now achieved the conversion of 2-methylquinoline into a 2,3-disubstituted quinoline, although the number of steps involved makes the route uneconomic in most cases. A possible mechanism for the formation of compound (**20**) is shown in Scheme 2.



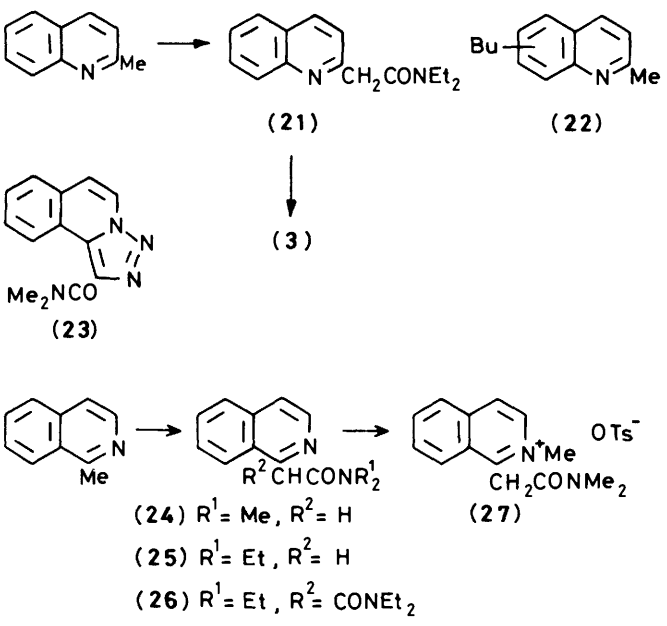
Scheme 2.

Another improvement to our original procedure for the conversion of triazoloquinolines to 2,3-disubstituted quinolines was achieved by a more direct synthesis of the amide (**3**). Treatment of 2-quinolylmethyl-lithium with *N*,*N*-diethylcarbamoyl chloride gave, in 70% yield, the 2-quinolylacetamide (**21**). A number of minor products were obtained, one identified by ^{1}H n.m.r. spectroscopy and elemental analysis as a 2-methyl-*x*-butylquinoline (**22**). The quinolylacetamide (**21**) was converted by treatment with tosyl azide and a base, the route used by Regitz[9] to prepare triazolopyridines, into the triazoloquinolylamide (**3**) in 34% yield; enough starting acetamide (**21**) could be recovered to indicate that conversion was over 50% based on the starting material used.

We have also attempted to use this sequence to obtain the triazoloisoquinoline amide (**23**). Reaction between the lithium derivative of 1-methylisoquinoline and *N*,*N*-dimethylcarbamoyl

Table. ^{1}H N.m.r. data of triazoloisoquinolines ($CDCl_3$ solutions)

Compd.	Substituent	Chemical shifts (δ in p.p.m.) 1-H	5-H	6-H	7-H 8-H 9-H	10-H	Other	*J* Values (Hz)
(4)	None	8.3 (s)	8.4 (d)	7.1 (d)	6.9—7.7 (m)	7.9—8.2 (m)		$J_{5,6}$ 8
(5)	1-NO_2		8.5 (d)	7.4 (d)	7.7—7.9 (m)	9.2—9.5 (m)		$J_{5,6}$ 7
(6)	1-Br		8.2 (d)	7.0 (d)	7.3—7.6 (m)	8.4—8.6 (m)		$J_{5,6}$ 8
(9)	5-(4-$MeOC_6H_4CHOH$)	8.4		7.0 (s)	7.4—7.7 (m)	8.0—8.2 (m)	6.9 (2 H, d, 3′- and 5′-H) and 7.4—7.7 (2 H, d, 2′- and 6′-H)	
(10)	5-$C(OH)Me_2$	8.2		7.0 (s)	7.3—7.6 (m)	7.7—8.0 (m)	1.9 (6 H, s), 5.3 (1 H, OH)	
(11)	5-$CONEt_2$	8.4		7.2 (s)	7.2—7.8 (m)	8.0—8.2 (m)	1.1—1.4 (6 H, t) 3.0—3.4 (2 H, q) 3.5—3.9 (2 H, q)	J_{CH_2Me} 7
(12)	5-$SiMe_3$	8.4		7.2 (s)	7.4—7.8 (m)	8.0—8.2 (m)	0.5 (9 H, s)	
(13)	1,5-$(SiMe_3)_2$			7.3 (s)	7.4—7.8 (m)	8.2—8.4 (m)	0.5 (9 H, s), 0.6 (9 H, s)	
	5-Deuterio	8.3 (s)		7.1 (s)	6.9—7.7 (m)	7.9—8.2 (m)		



chloride gave two products. One was the isoquinolylacetamide (**24**) (47%), the ^{1}H n.m.r. spectrum of which was notable for two signals due to non-equivalent methyl groups. The second product was unstable, but appeared to be an addition product of 1-methylisoquinoline, butyl-lithium, and dimethylcarbamoyl chloride. Reaction between 1-methylisoquinoline and diethylcarbamoyl chloride with an excess of butyl-lithium also gave a mixture. One product was the isoquinolylacetamide (**25**), in low yield. The other fully characterized product was the diamide (**26**), but there was a substantial amount of methylisoquinoline, and a product very similar in spectroscopic properties to the addition product from the dimethylcarbamoyl chloride. One attempt to convert the isoquinolylacetamide (**24**) into triazoloisoquinoline (**23**), using tosyl azide and sodium methoxide, gave only the quaternary salt (**27**), and some methyl toluenesulphonate. A similar result was obtained when a methyl 2-pyridylacetate was treated with tosyl azide and sodium methoxide.[3]

Experimental

All m.p.s were determined on a Kofler heated stage and are uncorrected. U.v. spectra were recorded in solutions in 95% ethanol, and n.m.r. spectra in $CDCl_3$, unless otherwise stated; i.r. spectra were for KBr discs unless otherwise stated. Chromatography was by column (alumina or silica), preparative plate (Merck silica PF_{254}, 20 × 20, or 20 × 40 cm), or Chromatotron (Merck silica PF_{254}, 2 mm plates). All lithations were performed under an atmosphere of nitrogen or argon. Light petroleum had b.p. 60—80 °C unless otherwise stated.

1-*Methylisoquinoline*.—This compound was prepared as described by Pictet and Gams[6] except that the reduction of *N*-acetyl-ω-aminoacetophenone was performed in methanol solution, using sodium borohydride (excess). The yield of *N*-acetyl-β-hydroxy-β-phenylethylamine was 82%.

1,2,3-*Triazolo*[5,1-a]*isoquinoline* (**4**).—This compound was prepared in 34% yield by the method of Abramovitch and Takaya,[5] m.p. 110—111 °C (lit.,[5] 110—111 °C).

1-*Nitro*-1,2,3-*triazolo*[5,1-a]*isoquinoline* (**5**).—To a vigorously stirred mixture of acetic anhydride (6 ml) and nitric acid (fuming, 2 ml) at 0 °C was added the triazoloisoquinoline (**4**) (0.3 g). Stirring was continued at room temperature (1 h) after which the mixture was poured into ice–water (40 ml) and the solid product filtered off. Recrystallization from chloroform–hexane gave the 1-*nitrotriazoloisoquinoline* (**5**), m.p. 199 °C (Found: C, 56.3; H, 2.55; N, 25.9. $C_{10}H_6N_4O_2$ requires C, 56.05; H, 2.8; N, 26.15%); the ^{1}H n.m.r. data for triazoloisoquinolines are in the Table; *m/z* 214 (M^+), 128 [M − (N=N–CNO_2), 75%].

1-*Bromo*-1,2,3-*triazolo*[5,1-a]*isoquinoline* (**6**).—(a) A solution of bromine (0.3 g) in carbon tetrachloride (10 ml) was added dropwise to a stirred solution of triazoloisoquinoline (0.2 g) in dichloromethane (6 ml) at room temperature. Stirring was continued (1 h) during which time a colourless solid separated. The solid was filtered off and found to be almost pure *bromotriazoloisoquinoline* (**6**) (0.26 g, 88%), m.p. 136 °C (cyclohexane) (Found: C, 48.65; H, 2.1; N, 17.0. $C_{10}H_6BrN_3$ requires C, 48.4; H, 2.4; N, 16.95%).

(b) A similar bromination at 70 °C p bromo compound (**6**) in 65% yield.

Acid Hydrolysis of Compound (**4**).—A solution of triazoloisoquinoline (**4**) (0.2 g) in 2N-sulphuric acid (20 ml) was boiled (3 h). The cooled solution was basified with aqueous sodium hydrogen carbonate and extracted with dichloromethane. The dried organic solution was evaporated and the residue purified by p.l.c. (eluant ethyl acetate) to give 1-hydroxymethylisoquinoline (**7**) (0.12 g, 64%), m.p. 78—79 °C (hexane) (lit.,[9,10]

77—79 °C); δ 5.1 (2 H, s), 5.3—5.7 (1 H, exch. D_2O, OH), 7.3—7.9 (5 H, m), and 8.3 (1 H, d, *J* 7 Hz, 3-H).

General Procedure for Lithiation of Triazoloisoquinoline (**4**).—To a magnetically stirred mixture of butyl-lithium (2 ml of a 1.5M solution in hexane) and di-isopropylamine (0.26 g) under nitrogen or argon at −40 °C was added by syringe a solution of triazoloisoquinoline (0.4 g) in anhydrous ether (40 ml). After 1 h, during which a deep red colour developed, the co-reactant was added, causing a colour change to yellow. The mixture was allowed to come to room temperature and was then stirred for 7 h; subsequently it was hydrolysed by a mixture of ammonium hydroxide and ammonium chloride. The purification procedure is described for each new compound.

5-(α-*Hydroxy*-4-*methoxybenzyl*)-1,2,3-*triazolo*-[5,1-a]*isoquinoline* (**9**). The co-reagent was anisaldehyde. The *methoxyphenyl alcohol* (**9**) was isolated by filtration, and recrystallized from benzene (0.5 g, 70%), m.p. 151—153 °C (Found: C, 70.65; H, 4.8; N, 13.65. $C_{18}H_{15}N_3O_2$ requires C, 70.8; H, 4.9; N, 13.75%); $\nu_{max.}$ 3 200—3 600 cm^{-1}; *m/z* 305 (M^+).

5-(2-*Hydroxypropan*-2-*yl*)-1,2,3-*triazolo*[5,1-a]*isoquinoline* (**10**). The co-reagent was acetone. The ethereal extracts from the hydrolysis mixture were evaporated and the residue separated by p.l.c. (eluant dichloromethane). The *hydroxypropyltriazoloisoquinoline* (**10**) was recrystallized from cyclohexane, m.p. 134—136 °C (0.23 g, 45%) (Found: C, 68.35; H, 5.8; N, 18.1. $C_{13}H_{13}N_3O$ requires C, 68.7; H, 5.75; N, 18.5%); $\nu_{max.}$ 3 300—3 600 cm^{-1}.

N,N-*Diethyl*-1,2,3-*triazolo*[5,1-a]*isoquinoline*-5-*carboxamide* (**11**). The co-reagent was *N,N*-diethylcarbamoyl chloride; the reaction was carried out with 0.8 g of triazoloisoquinoline. The hydrolysis mixture was extracted with ethyl acetate, the solution dried, and evaporated to give a crude residue (1.35 g). Purification on a silica column, eluting with increasing proportions of ethyl acetate in hexane gave the *amide* (**11**) (0.72 g, 57%), m.p. 118—119 °C (from cyclohexane) (Found: C, 66.9; H, 5.75; N, 20.7. $C_{15}H_{16}N_4O$ requires C, 67.15; H, 5.95; N, 20.9%).

5-*Trimethylsilyl*-1,2,3-*triazolo*[5,1-a]*isoquinoline* (**12**) *and* 1,5-*bis*(*trimethylsilyl*)-1,2,3-*triazolo*[5,1-a]*isoquinoline* (**13**). The co-reagent was trimethylsilyl chloride; 0.35 g of triazoloisoquinoline was used. Ethereal extracts from the hydrolysis mixture were dried, filtered, and evaporated. The crude residue (0.54 g) was purified on a silica column, eluant dichloromethane. The first compound eluted was the 1,5-*disilyltriazoloisoquinoline* (**13**) as an oil (0.15 g, 23%) (Found: C, 61.9; H, 7.7.; N, 13.1. $C_{16}H_{23}N_3Si_2$ requires C, 61.35; H, 7.35; N, 13.4%). The second compound eluted was the *monosilyl derivative* (**12**), m.p. 92—94 °C (from pentane) (0.3 g, 60%) (Found: C, 64.6; H , 6.4; N, 17.3. $C_{13}H_{15}N_3Si$ requires C, 64.75; H, 6.2; N, 17.45%). The third material eluted was the triazoloisoquinoline (**4**) (0.4 g, 11%).

Hydrolytic Ring Opening of the Alcohol (**9**).—A solution of the triazoloisoquinolinemethanol (**9**) (0.4 g) in methanol (10 ml) with 1M-sulphuric acid (40 ml) was boiled (5 h). The cooled solution was neutralized (saturated aqueous $NaHCO_3$) and extracted with dichloromethane. The organic extracts were treated with anhydrous Na_2SO_4, filtered, and evaporated. The crude products were separated on a Chromatotron (eluted with light petroleum with increasing proportions of ethyl acetate). Two bands were observed. The first band eluted was 1-*hydroxymethyl*-3,(α-4-*dimethoxybenzyl*)*isoquinoline* (**15**) (0.06 g, 15%) (Found: C, 73.65; H, 5.9; N, 4.6. $C_{19}H_{19}NO_3$ requires C, 73.75; H, 6.2; N, 4.55%); $\nu_{max.}$ 3 200—3 500, 1 250, 1 170, 1 090, and 1 030 cm^{-1}; δ 3.4 (3 H, s), 3.7 (3 H, s), 4.4—4.7 (1 H, br s, exch. D_2O, OH), 5.1 (2 H, s, CH_2OH), 5.4 (1 H, s, CHOMe), 6.7 (2 H, d, 3′- and 5′-H), and 7.2—7.8 (7 H, m). The second band was 1-*hydroxymethyl*-3-(α-*hydroxy*-4-*methoxybenzyl*)*isoquinoline* (**14**) (0.2 g, 52%), m.p. 103—104 °C (from light petroleum, b.p. 40—60 °C) (Found: C, 73.45; H, 5.5; N, 4.65. $C_{18}H_{17}NO_3$ requires C, 73.2; H, 5.75; N, 4.75%); $\nu_{max.}$($CHCl_3$) 3 300—3 600, 1 170, and 1 080 cm^{-1}; δ 3.7 (3 H, s), 4.4—4.7 (2 H, br s, exch. D_2O, 2 × OH), 5.0 (2 H, s, CH_2OH), 5.9 (1 H, s, CHOH), 6.7 (2 H, d, 3′- and 5′-H), and 7.2—7.8 (7 H, m).

Reaction of 4-(α-*Hydroxy*-4-*methoxybenzyl*)-1,2,3-*triazolo*-[1,5-a]*quinoline*-3-*carboxylic Acid with Glacial Acetic Acid*.—A solution of the acid (**19**) (0.05 g) in glacial acetic acid (10 ml) was boiled for 10 days. The solvent was evaporated under reduced pressure and the residue basified and extracted with dichloromethane; the solvent was evaporated and the residue sublimed (140 °C/0.01mmHg) to give 1-*methoxyphenyl*-1,3-*dihydrofuro*[3,4-b]*quinoline* (**20**) (0.03 g, 75%), m.p. 107—109 °C (Found: C, 77.4; H, 5.75; N, 5.15. $C_{18}H_{15}NO_2$ requires C, 77.95; H, 5.45; N, 5.05%); δ 3.8 (3 H, s), 5.25 (1 H, dd, *J* 1 and 13 Hz, 3a-H), 5.35 (1 H, dd, *J* 1 and 13 Hz, 3b-H), 6.27 (1 H, d, *J* 1 Hz, 1-H), 6.95 (2 H, d, *J* 8.8 Hz, 3′-and 5′-H), 7.25 (1 H, s, 10-H), 7.26 (2 H, d, *J* 8.8 Hz, 2′- and 6′-H), 7.3—7.8 (3 H, m), and 8.09 (1 H, br d, *J* 8 Hz, 5-H).

N,N-*Diethyl*-2-*quinolylacetamide* (**21**).—A solution of freshly distilled 2-methylquinoline (20 g) in anhydrous ether (200 ml) under argon, was treated at room temperature with butyl-lithium (1M in hexane; 160 ml); stirring was continued for 1.5 h. The solution was cooled to −40 °C and a solution of *N,N*-diethylcarbamoyl chloride (17 g) in anhydrous ether (120 ml) was slowly added. After addition the mixture was allowed to come to room temperature, and then stirred overnight. Hydrolysis with ammonia–ammonium chloride was followed by extraction with ether. The combined ethereal extracts were treated with anhydrous $MgSO_4$, filtered, and evaporated. The crude product (36.5 g) was purified on an alumina column (activity IV) using light petroleum with increasing quantities of ethyl acetate. The main product was the *diethylamide* (**21**) (23.6 g, 70%) (Found: C, 74.15; H, 7.8; N, 11.65. $C_{15}H_{18}N_2O$ requires C, 74.4; H, 7.45; N, 11.55%); δ 1.1 (6 H, t, CH_2Me), 3.1—3.6 (4 H, dq, CH_2Me), 4.0 (2 H, s), and 7.2—8.1 (6 H, m). The first fraction from the column was butyl(methyl)quinoline (**22**), b.p. 95 °C/0.3 mmHg; δ 0.8—2.1 (7 H, m), 2.8 (3 H, s), 2.8—3.1 (2 H, m), 7.15 (1 H, d, *J* 8 Hz, 3-H), 7.3—7.6 (3 H, m), and 7.9 (1 H, d, *J* 8 Hz, 4-H).

Conversion of N,N-*Diethyl*-2-*quinolylacetamide into* N,N-*Diethyl*-1,2,3-*triazolo*[1,5-a]*quinoline*-3-*carboxamide* (**3**).—A solution of the acetamide (**21**) (20 g) in ethanol (35 ml) was added dropwise, under nitrogen to a stirred solution of sodium (1.9 g) in anhydrous ethanol (120 ml), maintained at 15—20 °C. The mixture was stirred for 3.5 h and then tosyl azide (17.9 g) was added; the solution turned green and then orange. After further stirring at room temperature (0.5 h), water (100 ml) was added, and the mixture extracted with dichloromethane. The dichloromethane extracts were dried, filtered, evaporated, and the residue chromatographed on alumina (activity IV). Elution with light petroleum and increasing amounts of ethyl acetate gave first some ethyl toluenesulphonate and then the carboxamide (**3**) (7.5 g, 34%). Varying quantities of the acetamide (**21**) were recovered; in some cases the yield of amide (**3**) based on unrecovered acetamide (**21**) was 70%.

N,N-*Dimethyl*-1-*isoquinolylacetamide* (**24**).—This compound was prepared as described for compound (**21**) from 1-methylisoquinoline (1 g) and *N,N*-dimethylcarbamoyl chloride (0.75 g); two compounds were obtained by chromatography on alumina (activity IV), eluting with ethyl acetate–hexane (1:4 to 1:1). The *amide* (**24**) crystallized from light petroleum (b.p.

40—60 °C), m.p. 104—107 °C (0.7 g, 47%) (Found: C, 72.95; H, 6.7; N, 12.65. $C_{13}H_{14}N_2O$ requires C, 72.85; H, 6.6; N, 13.05%); $\nu_{max.}$ 1 650 cm^{-1}; δ 2.98 (3 H, s), 3.16 (3 H, s), 4.4 (2 H, s), 7.75—7.9 (4 H, m), 8.3—8.4 (1 H, m, 8-H), and 8.45 (1 H, d, *J* 6 Hz, 3-H). The second product proved very unstable; the i.r. showed amide CO at 1 660 cm^{-1}; δ 0.6—1.9 (11 H, m), 2.8 (6 H, s, $CONMe_2$), 4.8 (1 H, t, *J* 7 Hz, $CHCH_2$), 6.25 (1 H, d, *J* 7.3 Hz, 3-H), 6.35 (1 H, dd, *J* 7.3 and 1 Hz, 4-H), and 6.9—7.2 (3 H, m).

N,N-*Diethyl*-1-*isoquinolylacetamide* (**25**) *and* N,N,N′,N′-*tetraethyl*-1-*isoquinolylmethylenedicarboxamide* (**26**).—This compound was prepared as described for compound (**21**) from 1-methylisoquinoline (3.26 g), diethylcarbamoyl chloride (3.075 g), and an excess of butyl-lithium. The crude product, treated with ether, gave the solid *diacetamide* (**26**) which recrystallized from hexane (0.7, 10%), m.p. 142—144 °C (Found: C, 70.3; H, 7.95; N, 12.15. $C_{20}H_{27}N_3O_2$ requires C, 70.4; H, 7.9; N, 12.3%); δ 0.8 (12 H, overlapping t, NEt), 3.1—3.7 (8 H, overlapping q, NEt), 5.8 (1 H, s, CHCO), 7.6—7.8 (4 H, m), 8.2—8.3 (1 H, m, 8-H), 8.4 (1 H, d, *J* 5 Hz, 4-H). The second product was the major one, but could not be adequately purified. The third product was the diethylacetamide (**25**), a yellow oil (0.3 g); δ 0.8—1.3 (6 H, 2 t, NCH_2Me), 3.0—3.6 (4 H, 2 q, NCH_2Me), 4.3 (2 H, s, CH_2CONEt_2), 7.3—7.6 (4 H, m), 8.0—8.3 (1 H, m, 8-H), and 8.3 (1 H, d, *J* 5 Hz, 4-H).

Reaction Between N,N-*Dimethyl*-1-*isoquinolylacetamide and Tosyl Azide*.—Using the procedure described[3] for methyl 2-pyridylacetate, and sodium methoxide as base, the main product was 1-(N,N-*dimethylcarbamoylmethyl*)-2-*methyl-isoquinolinium toluene*-p-*sulphonate* (**27**), m.p. 189—191 °C (from chloroform–carbon tetrachloride) (60%) (Found: C, 63.0; H, 6.0; N, 7.0. $C_{21}H_{24}N_2O_4S$ requires C, 62.9; H, 6.05; N, 7.0%); δ 2.2 (3 H, s), 2.9 (3 H, s), 3.3 (3 H, s), 4.5 (3 H, s), 5.0 (2 H, s), 6.9 (2 H, d), 7.5 (2 H, d), 7.7—7.9 (6 H, m), 8.1—8.3 (1 H, m), and 8.5 (1 H, d).

Acknowledgements

Our thanks are due to John Clews for skilled technical assistance.

References

1 G. Jones and D. R. Sliskovic, *Tetrahedron Lett.*, 1980, 4529.
2 G. Jones and D. R. Sliskovic, *J. Chem. Soc., Perkin Trans. 1*, 1982, 967
3 B. Abarca, D. J. Hayles, G. Jones, and D. R. Sliskovic, *J. Chem. Res.*, 1983 (*S*), 144; (*M*), 1341.
4 B. Abarca, E. Gomez-Aldaravi, and G. Jones, *J. Chem. Res.*, 1984, (*S*) 140; (*M*), 1430.
5 R. A. Abramovitch and T. Takaya, *J. Org. Chem.*, 1972, **37**, 2022.
6 A. Pictet and A. Gams, *Ber.*, 1910, **43**, 2384.
7 G. A. Russell and S. A. Weiner, *J. Org. Chem.*, 1966, **31**, 248.
8 G. Jones and D. J. Mouat, unpublished results.
9 M. Regitz and A. Liedhegener, *Chem. Ber.*, 1966, **99**, 2918.
10 L. R. Walters, I. C. Mineo, and R. S. Kripowicz, *J. Org. Chem.*, 1964, **29**, 980.
11 B. R. Brown, D. Ll. Hamick, and B. H. Thewlis, *J. Chem. Soc.*, 1951, 1145.

Received 31*st December* 1984; *Paper* 4/2172