Diazines. IX. Metalation of 2-Chloro, 2-Methoxy and 2-Pivaloylaminoquinoxaline

A. Turck, N. Ple, V. Tallon and G. Queguiner*

Laboratoire de Chimie Organique Fine et Hétérocyclique,
URA 1429, INSA-IRCOF, BP 08,
76131 Mt St Aignan Cedex, France

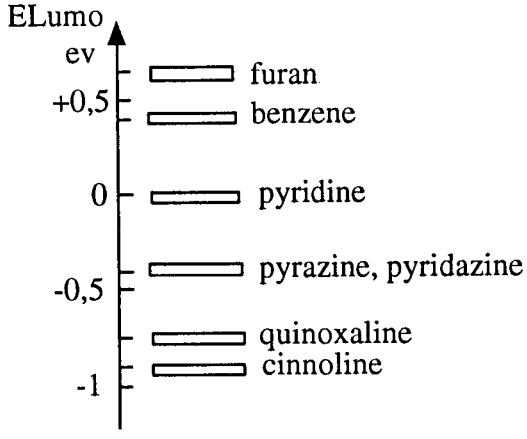
Received April 19, 1993

The lithiation of 2-chloro, 2-methoxy and 2-pivaloylaminoquinoxaline was studied. In the case of 2-chloro and 2-methoxyquinoxaline the simultaneous formation of dimers could not be avoided. The resulting lithio derivatives were reacted with carbonyl compounds and iodine. Yields in excess of 50% were obtained.

J. Heterocyclic Chem., **30**, 1491 (1993).

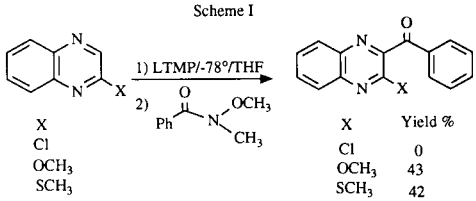
Following studies on the metalation of diazines [1-8], the close series of benzodiazines (quinoxaline, phthalazine, cinnoline and quinazoline) represents an interesting challenge. Nevertheless a glance at the energy value of the Lumo of some aromatic compounds (Table I) (MNDO calculation) indicates that the competitive reaction of nucleophilic addition will compete still more seriously with the metalation in the case of benzodiazines, Table I.

Table I



Quinoxaline derivatives have been chosen as they are easy to prepare from the commercially available 2-hydroxyquinoxaline and lead to 2,3-disubstituted quinoxalines which are not so easy to prepare by other routes. Moreover, quinoxaline derivatives have important uses in agriculture and as pharmaceuticals [9]. We describe here the metalation of 2-chloroquinoxaline **1**, 2-methoxyquinoxaline **2** and 2-pivaloylaminoquinoxaline **3**. During the course of our work a paper dealing with the synthesis of quinoxaline ketones was published [10]. The authors reacted *N*-methoxy-*N*-methylbenzamide with lithio derivatives of 2-chloro, 2-methoxy and 2-thiomethylquinoxaline (Scheme I). With 2-chloroquinoxaline the reaction failed to afford the expected ketone.

Scheme I

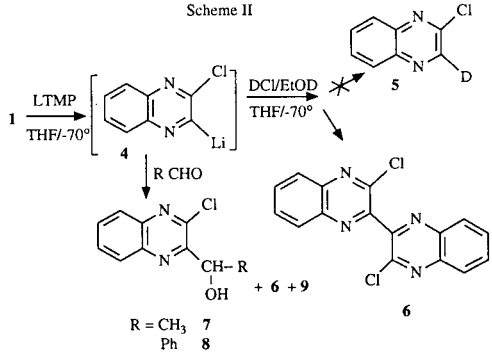


[a] LTMP : lithium 2,2,6,6-tetramethylpiperidide

1) Metalation of 2-Chloroquinoxaline **1**.

The first reactions were performed following the procedure used with 2-chloropyrazine [1] and with deuterium chloride as the electrophile (Scheme II).

Scheme II



The use of deuterium chloride as the electrophile allowed us to observe the disappearance of H_3 in the ^1H nmr spectrum (H_3 is very easy to identify as it provides a singlet 1 ppm removed from the benzene hydrogens) as was expected for **5** but the melting point of 226° could not be that of **5** because **1** melts under 50°. Mass spectroscopy indicated a molecular weight of 327 and a micro analysis of the product confirmed the formula **6** which is a "*dimer*" of compound **1**. It was also found that the yield of compound **6** was lower when the metalation time was increased

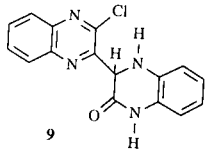
Table II

R	LTMP	Yield of alcohol	Yield of 6	Yield of 9
CH_3	1,2	**7** (11%)	21%	46%
CH_3	2,2	**7** (66%)	3%	16%
Ph	1,2	**8** (22%)	12%	–
Ph	2,2	**8** (52%)	20%	–

(15 minutes, yield 59%; 1 hour, 40 minutes, yield 34%). The obtaining of dimer **6** indicated that the metalation reaction took place as a first step. Therefore carbon electrophiles were tested (Table II).

Compound **9**.

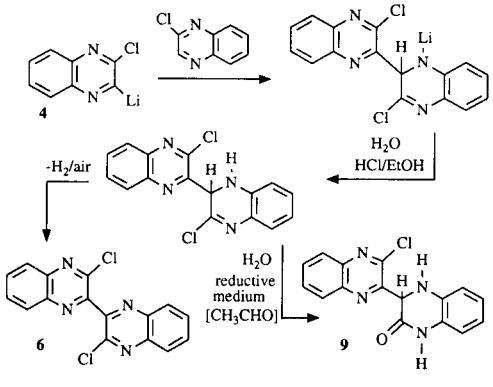
A complete analysis of **9** which included ir, ^1H nmr, ^{13}C nmr, mass spectra and elemental analysis lead to the following structure:



9

This compound was formed by addition of the lithio derivative **4** with **1** followed by replacement of the chlorine atom by OH during the hydrolysis of the reaction mixture, (Scheme III).

Scheme III

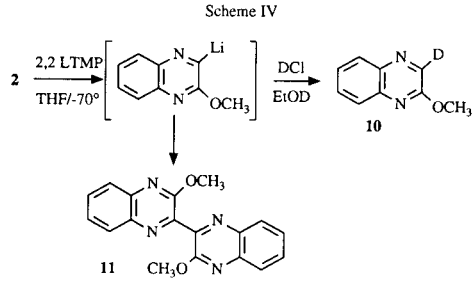


The use of acetaldehyde as the electrophile in large excess prevented the oxidation of the intermediate dihydro compound. In order to avoid nucleophilic addition, a metalation by equilibrium shift was tested with trimethylchlorosilane as the electrophile. The simultaneous introduction of the electrophile and of the quinoxaline to the metalating agent ought to prevent the nucleophilic attack of **1** by the lithio derivative **4**. But no silylated derivative was isolated, only **9** (42%) and **1** (32%) were obtained. From these experimental results one can assume that the nucleophilic addition is a very fast reaction which cannot be completely avoided in this case. Nevertheless we could achieve the metalation of 2-chloroquinoxaline with yields in excess of 50% using benzaldehyde or acetaldehyde as the electrophile. As these experimental results with a chlorine atom as an *ortho* directing group were not truely satisfactory another group was tried with a better electron releasing group to counteract the lowering of the lumo energy.

2) Metalation of 2-Methoxyquinoxaline **2**.

First trials were performed with deuterium chloride as the electrophile with 2,2 equivalents of metalating agents as for methoxypyrazines [4] (Scheme IV).

Scheme IV



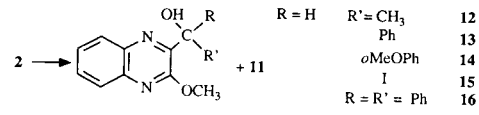
Compound **10** and **2** were easily separated from **11** by column chromatography and the percentage of deuterio product **10** was evaluated by ^1H nmr.

Table III

Metalation time	Yield of dimer **11**	Yield of **2** + **10**	Percent of **10**	Calculated yield of **10**
15 minutes	10%	76%	83%	63%
2 hours	23%	57%	92%	52%

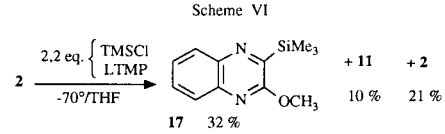
It must be noticed that the metalation reaction was fast and that the amount of dimer **11** increased with the time but was much lower than with 2-chloroquinoxaline. Iodine, acetaldehyde, benzaldehyde and benzophenone were tested as electrophiles and an optimisation was attempted by variation of the parameters of the reaction: amount and nature of the metalating agent, temperature, metalation time, solvent, electrophile (Scheme V, Table IV).

Scheme V



In order to avoid the formation of dimer **11** and as attempted previously with 2-chloroquinoxaline, a metalation by equilibrium shift was performed with chlorotrimethylsilane as the electrophile (Scheme VI).

Scheme VI



Even in that case a notable amount of dimer was present but we could isolate a substantial amount of silylated derivative.

Table IV

Entry	Solvent	Electrophile	Metalation Agent	Equiv Nbr	Temp	Metalation Time	Yield of dimer	No.	yield of alcohol or iodo deriv	2 rec
1	THF	CH_3CHO	LTMP	1.2	-70°	1 h	–		–	100%
2	"	"	"	2.2	"	15 min	29%	12	14%	0%
3	"	"	"	"	"	1 h	26%	"	42%	–
4	"	"	"	"	"	2 h	23%	"	46%	–
5	"	"	"	4.4	"	"	21%	"	63%	–
6	"	"	"	1.1	0°	1 h	50%	"	17%	–
7	"	"	LDA	2.2	-70°	2 h	44%	"	–	35%
8	Ether	"	LTMP	2.2	"	"	20%	"	24%	11%
9	THF	"	"	"	-100°	"	37%	"	39%	–
10	"	"	*t*-BuOK LTMP	2.2	-70°	"	53%	"	12%	5%
11	"	"	*t*-BuOK LDA	"	"	"	27%	"	–	46%
12	"	PhCHO	LTMP	"	"	15 min	44%	13	44%	–
13	"	"	"	"	"	2 h	29%	–	70%	–
14	"	PhCOPh	"	"	"	1 h	9%	14	58%	–
15	"	I_2	"	"	"	1 h	15%	15	50%	–
16	"	O Me OPh CHO	"	4	"	2 h	17%	16	60%	–

[a] LDA: lithium diisopropylamide.

Remarks:

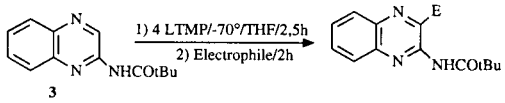
Whatever the electrophile or the metalation conditions may be the formation of dimer **11** could not be avoided but could only be limited.

As the metalation time was increased the yield of the dimer decreased a little (Table IV entries 2, 3, 4, and 12, 13) but the yield of alcohol increased greatly.

3) Metalation of 2-Pivaloylaminoquinoxaline **3** (Scheme VII).

Compound **3** was synthesized in a 96% yield by reaction of 2-aminoquinoxaline with pivaloyl chloride.

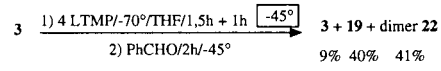
Scheme VII



3

	E	Yield	3 recovered
18	$-CH(OH)-CH_3$	63 %	29 %
19	$-CH(OH)-Ph$	65 %	29 %
20	— I	57 %	14 %
21	— COOH	32 %	24 % + 14 % dimer **22**

Under these conditions no dimer was found except for carbonic anhydride but a lot of starting material **3** was recovered so an experiment at a higher temperature was performed.



The amount of starting material was decreased but so was the yield of **19** and dimer **22** was now present.

Conclusion:

The metalation of 2-chloro and 2-methoxyquinoxaline has been studied and experimental processes leading to yields better than 50% were found. In the case of 2-pivaloylaminoquinoxaline no dimer was present at low temperature except in one case and the yields were satisfactory as the other recovered product was mainly starting material.

EXPERIMENTAL

All reagents were of commercial quality and were purchased from Aldrich Chemical Co. or Janssen Pharmaceutica. All solvents were freshly distilled. Tetrahydrofuran was dried by boiling with benzophenone/sodium and its water content (> 50 ppm) was determined by the modified Karl-Fischer method.

Metalations were performed under an argon atmosphere. Reagents were handled with syringes through septa.

Melting points were determined on a Kofler hot stage and are uncorrected. Microanalyses were performed on a Carlo Erba CHNOS 1106 apparatus. The ^1H nmr spectra were recorded on a Varian EM 360 L spectrometer in deuteriochloroform with tetramethylsilane as the internal standard or in deuterated dimethyl sulfoxide with hexamethyldisiloxane. The ir spectra were recorded on a Beckman 4250 spectrometer. All ir spectra performed in potassium bromide.

Preparation of Reagents.

2-Chloroquinoxaline (**1**) and 2-methoxyquinoxaline (**2**) were obtained by standard preparation according to the procedures in the literature.

2-Pivaloylaminoquinoxaline (**3**).

2-Aminoquinoxaline prepared according to the method of Wolf [11] (1.15 g, 7.93 mmoles) was dissolved in tetrahydrofuran (40 ml), triethylamine (2.8 ml, 19.04 mmoles) was added. After cooling to 0°, pivaloylchloride (2.4 ml, 19.04 mmoles) was slowly introduced into the solution, and stirred for 24 hours at room temperature. The mixture was then hydrolysed with water (20 ml). After evaporation of the organic solvent, it was extracted with dichloromethane (3 x 40 ml). The organic layer was dried (magnesium sulfate) and evaporated. The crude product was purified by chromatography on silica gel with a mixture dichloromethane/ethyl acetate (9/1) as eluant; 1.75 g (96%) of a white powder was obtained, mp 92°; ^{1}H nmr (deuteriochloroform): δ 1.39 (s, 9H, *t*-Bu), 7.74 (m, 3H, H_{5-7}), 8.08 (d, 1H, H_8), 8.19 (s, 1H, NH), 9.86 (s, 1H, H_3); ir: ν 3330, 2980, 1690, 1570, 1490, 1420, 1315, 1230 cm^{-1}.

Anal. Calcd. for $C_{13}H_{15}N_3O$ (M = 229.3): C, 68.04; N, 18.32; H, 6.54. Found: C, 68.09; N, 18.16; H, 6.59.

General Procedure for Metalation.

A solution of butyllithium (1.6 *M* in hexane) was added to cold (−78°), stirred, anhydrous tetrahydrofuran (30 ml) under an atmosphere of dry argon. 2,2,6,6-Tetramethylpiperidine was added and the mixture was allowed to stand at 0° for 30 minutes. The 2-substituted quinoxaline dissolved in tetrahydrofuran (5 ml) was then added at −78°, and the solution was stirred at −78° for a time t_1. The electrophile was introduced and stirring was continued for a time t_2 at −78°. Hydrolysis was then carried out at −78° using a mixture of 35% aqueous hydrochloric acid (2 ml), ethanol (3 ml) and tetrahydrofuran (5 ml). The solution was then gently warmed to room temperature, made slightly basic with a saturated sodium hydrogen carbonate solution and evaporated nearly to dryness. The residue was extracted with dichloromethane (3 x 50 ml). The organic extract was dried over magnesium sulfate, then evaporated. The crude product was purified by column chromatography on silica gel.

3,3′-Dichloro-2,2′-biquinoxalinyl (**6**).

Metalation of 2-chloroquinoxaline (**1**) (165.1 mg, 1 mmole) according to the general procedure with *n*-butyllithium (0.8 ml, 1.25 mmoles) and 2,2,6,6-tetramethylpiperidine (0.2 ml, 1.25 mmoles), t_1 = 15 minutes, and deuteriolysis with a mixture of 0.5 ml of deuterium chloride and 0.3 ml of deuterated ethanol, after column chromatography with a 7/3 mixture of hexane and ethyl acetate, afforded 98.1 mg (59%) of a yellow solid, mp 226°; ^{1}H nmr (deuteriochloroform): δ 7.97 (m, 8H); ir: ν 3420, 1640-1550, 1255, 1170 cm^{-1}.

Anal. Calcd. for $C_{16}H_8N_4Cl_2$ (M = 327.18): C, 58.68; N, 17.12; H, 2.45. Found: C, 58.52; N, 16.87; H, 2.58.

(2-Chloro-3-quinoxalinyl)ethanol (**7**) and 3-(3-Chloro-2-quinoxalinyl)-3,4-dihydroquinoxalin-2(1*H*)-one (**9**).

Metalation of **1** (314.5 mg, 1.91 mmoles) according to the general procedure with *n*-butyllithium (2.6 ml, 4.20 mmoles) and 2,2,6,6-tetramethylpiperidine (0.71 ml, 4.20 mmoles), t_1 = 30 minutes; then reaction with acetaldehyde (1 ml), t_2 = 1 hour, and purification by chromatography with a 93/7 mixture of dichloromethane and ethyl acetate as eluant, gave 11.0 mg (3%) of **6**, 263.9 mg (66%) of a white solid **7**, mp 68°; ^{1}H nmr (deuteriochloroform): δ 1.58 (d, 3H, CH_3, J = 6 Hz), 4.27 (d, 1H, OH), 5.35 (q, 1H, CH, J = 6 Hz), 7.97 (m, 4H, H_{5-8}); ir: ν 3450, 2972, 1563, 1485, 1430, 1361, 1262, 1190-1009 cm^{-1}.

Anal. Calcd. for $C_{10}H_9ClN_2O$ (M = 208.6): C, 57.53; N, 13.42; H, 4.31. Found: C, 57.75; N, 13.08; H, 4.42.

Another fraction afforded 47.3 mg (16%) of an orange solid **9**, mp 255° dec; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 5.7 (s, 1H, CH), 6.73 (m, 5H, $H_{5'-8'}$ + NH), 8.0 (m, 4H, H_{5-8}), 10.75 [s, 1H, NH(CO)]; ir: ν 3350, 3050, 1685, 1500, 1040 cm^{-1}.

Anal. Calcd. for $C_{16}H_{11}N_4ClO$ (M = 310): C, 61.93; N, 18.06; H, 3.55. Found: C, 62.13; N, 17.91; H, 3.49.

(2-Chloro-3-quinoxalinyl)phenylmethanol (**8**).

Metalation of **1** (339.3 mg, 2.06 mmoles) according to the general procedure with *n*-butyllithium (2.8 ml, 4.53 mmoles) and 2,2,6,6-tetramethylpiperidine (0.72 ml, 4.53 mmoles), t_1 = 30 minutes, and reaction with benzaldehyde (460 µl, 4.53 mmoles), t_2 = 1.5 hours, gave after chromatography with a 8/2 mixture of dichloromethane and hexane, 67.4 mg (20%) of **6** and 289.9 mg (52%) of **8** as a white powder, mp 114°; ^{1}H nmr (deuteriochloroform): δ 5.18 (d, 1H, OH, J = 7 Hz), 6.15 (d, 1H, CH, J = 7 Hz), 7.32 (s, 5H, H phenyl), 7.93 (m, 4H, H_{5-8}); ir: ν 3400, 3050, 2920, 1560, 1490, 1450, 1350, 1250, 1190, 1125, 1040 cm^{-1}.

Anal. Calcd. for $C_{15}H_{11}N_2OCl$ (M = 270.72): C, 66.64; N, 10.37; H, 4.07. Found: C, 66.98; N, 10.36; H, 4.06.

2-Deuterio-3-methoxyquinoxaline (**10**) and 3,3′-Dimethoxy-2,2′-biquinoxalinyl (**11**).

Metalation of 2-methoxyquinoxaline (**2**) (346.0 mg, 2.16 mmoles) according to the general procedure with *n*-butyllithium (3 ml, 4.75 mmoles) and 2,2,6,6-tetramethylpiperidine (0.75 ml, 4.75 mmoles), t_1 = 15 minutes; and deuteriolysis with a mixture of 0.5 ml of deuterium chloride and 0.3 ml of deuterated ethanol, gave after purification by chromatography with a 7/3 mixture of hexane and ether as eluant, 262.8 mg (76%) of product which was a mixture of unreacted 2-methoxyquinoxaline (**2**) (17%) and deuterated product **10** (83%). The percentage was determinated by analysis of the nmr spectrum in which H_3 (8.45 ppm) is very easy to identify, mp <50°. Another fraction afforded 35.8 mg (10%) of **11** as a yellow powder, mp 175°; ^{1}H nmr (deuteriochloroform): δ 4.08 (s, 6H, OCH_3), 7.62 (t, 2H), 7.75 (t, 2H), 7.95 (d, 2H), 8.15 (d, 2H).

Anal. Calcd. for $C_{18}H_{14}N_4O_2$ (M = 318.33): C, 67.92; N, 17.61; H, 4.40. Found: C, 67.62; N, 17.39; H, 4.47.

(2-Methoxy-3-quinoxalinyl)ethanol (**12**).

Metalation of **2** (330.3 mg, 2.06 mmoles) according to the general procedure with *n*-butyllithium (2.9 ml, 4.54 mmoles) and 2,2,6,6-tetramethylpiperidine (0.77 ml, 4.54 mmoles), t_1 = 2 hours; reaction with acetaldehyde (1 ml), t_2 = 1 hour; and column chromatography with a 9/1 mixture of dichloromethane and ethyl acetate as eluant, afforded 74.3 mg (23%) of (**11**) and 194.7 mg 46% of a white powder **12**, mp 52°; ^{1}H nmr (deuteriochloroform): δ 1.55 (d, 3H, CH_3, J_1 = 6.5 Hz), 4.10 (s, 3H, OCH_3), 4.52 (d, 1H, OH, J_2 = 6.1 Hz), 5.15 (q, 1H, CH, J_1 = 6.5 Hz, J_2 = 6.1 Hz), 7.73 (m, 4H, H_{5-8}); ir: ν 3480, 3080, 2960, 1580, 1445, 1400, 1330, 1225, 1150, 1080 cm^{-1}.

Anal. Calcd. for $C_{11}H_{12}N_2O_2$ (M = 204.14): C, 64.66; N, 13.71; H, 5.88. Found: C, 64.60; N, 13.70; H, 5.95.

(2-Methoxy-3-quinoxalinyl)phenylmethanol (**13**).

Metalation of **2** (331.6 mg, 2.07 mmoles) according to the general procedure with *n*-butyllithium (2.9 ml, 4.55 mmoles) and 2,2,6,6-tetramethylpiperidine (0.72 ml, 4.55 mmoles), t_1 = 2 hours, and reaction with benzaldehyde (0.320 ml, 4.55 mmoles), t_2 = 2

hours, gave after column chromatography using a 6/4 mixture of hexane and ether as eluant, 95.5 mg (29%) of **11** and 386.1 mg (70%) of **13** as yellow crystals, mp 124°; ^{1}H nmr (deuteriochloroform): δ 3.89 (s, 3H, OCH_3), 5.2 (s, 1H, OH), 6.0 (s, 1H, CH), 7.49 (m, 9H, H_{5-8} + H phenyl); ir: ν 3250, 3050, 2920, 1575, 1450, 1325, 1220, 1050 cm^{-1}.

Anal. Calcd. for $C_{16}H_{14}N_2O_2$ (M = 266.3): C, 72.10; N, 10.51; H, 5.26. Found: C, 71.99; N, 10.29; H, 5.19.

(2-Methoxy-3-quinoxalinyl)-2-methoxyphenylmethanol (**14**).

Metalation of **2** (1.02 g, 6.37 mmoles) with lithium 2,2,6,6-tetramethylpiperidide (25.5 mmoles) according to the general procedure, t_1 = 2 hours, and reaction with orthoanisaldehyde (3.47 g, 25.5 mmoles), t_2 = 1.5 hours, and purification by column chromatography with a 7/3 mixture of hexane and ethyl acetate as eluant afforded 172.0 mg (17%) of dimer **11** and 1.13 g (60%) of a pale yellow solid **16**, mp 114°; ^{1}H nmr (deuteriochloroform): δ 3.8 (s, 3H, OCH_3 benz), 3.92 (s, 3H, OCH_3 quinox), 5.1 (d, 1H, OH, J = 7 Hz), 6.4 (d, 1H, CH, J = 7 Hz), 6.97 (m, 4H, H benz), 7.83 (m, 4H, H_{5-8}); ir: ν 3500, 3100, 2900, 1580, 1491, 1447, 1396, 1329, 1294, 1249, 1039 cm^{-1}.

Anal. Calcd. for $C_{17}H_{16}N_2O_3$ (M = 296.3): C, 68.92; N, 9.46; H, 5.41. Found: C, 68.58; N, 9.08; H, 5.36.

3-Iodo-2-methoxyquinoxaline (**15**).

Metalation of **2** (326.0 mg, 2.04 mmoles) according to the general procedure with *n*-butyllithium (2.8 ml, 4.49 mmoles) and 2,2,6,6-tetramethylpiperidine (0.70 ml, 4.49 mmoles), t_1 = 2 hours, reaction with iodine (1.2 g, 4.68 mmoles), t_2 = 2 hours, and purification by chromatography using a 9/1 mixture of dichloromethane and hexane as eluant afforded 48.2 mg (15%) of **11** and 287.7 mg (50%) of orange crystals **15**, mp 68°; ^{1}H nmr (deuteriochloroform): δ 4.18 (s, 3H, OCH_3), 7.76 (m, 4H, H_{5-8}); ir: ν 3060, 2950, 1570, 1445, 1400, 1360, 1330, 1070 cm^{-1}.

Anal. Calcd. for $C_9H_7N_2OI$ (M = 286.07): C, 37.77; N, 9.78; H, 2.45. Found: C, 38.00; N, 9.57; H, 2.44.

(2-Methoxy-3-quinoxalinyl)diphenylmethanol (**16**).

Metalation of **2** (326.0 mg, 2.04 mmoles) with 2,2,6,6-lithium tetramethylpiperidide (4.49 mmoles) prepared as described in the general procedure, t_1 = 1.45 hours, and reaction with benzophenone (821.5 mg, 4.5 mmoles), t_2 = 2 hours, gave after purification by column chromatography using a 15/85 mixture of ether and hexane as eluant 22.5 mg (8%) of **11** and 402.7 mg (58%) of a white powder **14**, mp 156°; ^{1}H nmr (deuteriochloroform): δ 3.8 (s, 3H, OCH_3), 6.43 (s, 1H, OH), 7.6 (m, 14H, H phenyl + H_{5-8}); ir: ν 3520, 3080, 2950, 1580, 1490, 1445, 1390, 1320, 1150 cm^{-1}.

Anal. Calcd. for $C_{22}H_{18}N_2O_2$ (M = 342.31): C, 77.12; N, 8.19; H, 5.26. Found: C, 77.09; N, 7.99; H, 5.21.

2-Methoxy-3-trimethylsilylquinoxaline (**17**).

A solution on *n*-butyllithium (2.9 ml, 4.7 mmoles) was added to cold (−30°) stirred, anhydrous tetrahydrofuran (30 ml) under dry argon. 2,2,6,6-Tetramethylpiperidine (0.74 ml, 4.7 mmoles) was then added and the solution warmed to 0° was kept at 0° for 30 minutes. It was then cooled to −78°. 2-Methoxyquinoxaline **2** (338.1 mg, 2.1 mmoles) and trimethylsilylchloride (0.6 ml, 4.7 mmoles) were introduced simultaneously, and stirring was continued at −78° for 2 hours. The mixture was then slowly hydrolysed with a mixture of 35% aqueous hydrochloric acid (1 ml), ethanol (4 ml) and tetrahydrofuran (5 ml), gently warmed to room temperature, neutralized with a saturated sodium hydrogen carbonate solution and evaporated nearly to dryness. The residue was extracted with dichloromethane (3 x 50 ml). The extract was dried over magnesium sulfate and evaporated. The crude product was purified by column chromatography on silica gel using a 3/7 mixture of dichloromethane and hexane as eluant, 70.7 mg (21%) of unreacted **2** were recovered, and it afforded 36.9 mg (11%) of dimer **11** and 154.7 mg (32%) of a colorless oil which was the silylated derivative **17**; ^{1}H nmr (deuteriochloroform): δ 0.43 (s, 9H, $Si(CH_3)_3$), 4.07 (s, 3H, OCH_3), 7.75 (m, 4H, H_{5-8}); ir: ν 3060, 2950-2900, 1575, 1550, 1445, 1250, 1140 cm^{-1}.

Anal. Calcd. for $C_{12}H_{16}N_2OSi$ (M = 232.4): C, 61.97; N, 12.05; H, 6.89. Found: C, 62.24; N, 11.88; H, 6.39.

(2-Pivaloylamino-3-quinoxalinyl)ethanol (**18**).

Metalation of 2-pivaloylaminoquinoxaline (**3**) (454.0 mg, 1.97 mmoles) with *n*-butyllithium (4.9 ml, 7.9 mmoles) and 2,2,6,6-tetramethylpiperidine (1.32 ml, 7.9 mmoles), t_1 = 1.5 hours, and reaction with acetaldehyde (1 ml), t_2 = 1 hour, afforded after chromatography with a 85/15 mixture of dichloromethane and ethylacetate as eluant, 131 mg (29%) of starting material **3** recovered and 342.0 mg (63%) of white crystals **18**, mp 204°; ^{1}H nmr (deuteriochloroform): δ 1.3 (s, 9H, *t*-Bu), 1.62 (d, 3H, CH_3, J = 6.6 Hz), 4.37 (q, 1H, CH, J = 6.6 Hz), 5.13 (s, 1H, OH), 7.8 (m, 4H, H_{5-8}), 9.8 (s, 1H, NH); ir: ν 3320-3230, 2960-2860, 1690, 1590, 1520, 1480, 1190 cm^{-1}.

Anal. Calcd. for $C_{15}H_{19}N_3O_2$ (M = 273.3): C, 65.86; N, 15.37; H, 6.95. Found: C, 66.23; N, 15.19; H, 6.99.

(2-Pivaloylamino-3-quinoxalinyl)phenylmethanol (**19**) and 3,3'-Dipivaloylamino-2,2'-biquinoxalinyl (**22**).

Metalation of **3** (419.1 mg, 1.83 mmoles) with lithium 2,2,6,6-tetramethylpiperidide (7.32 mmoles) according to the general procedure, t_1 = 2.5 hours, and reaction with benzaldehyde (0.75 ml, 7.32 mmoles), t_2 = 2 hours, gave after purification by chromatography with a 85/15 mixture of hexane and ethylacetate as eluant, 123.8 mg (29%) of **3** recovered and 395.1 mg (65%) of a yellow powder **19**, mp 215°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 1.07 (s, 9H, *t*-Bu), 6.0 (s, 1H, CH), 7.2 (s, 5H, H phenyl), 7.68 (m, 6H, OH + NH + H_{5-8}); ir: ν 3300, 3050-2960, 1685, 1510, 1480 cm^{-1}.

Anal. Calcd. for $C_{20}H_{21}N_3O_2$ (M = 335.4): C, 71.56; N, 12.52; H, 6.26. Found: C, 71.46; N, 12.47; H, 6.41.

If during the reaction with the metalating agent, the temperature was raised to −45° and the reaction with the electrophile was performed at the same temperature, the yield of **17** decreased to 40% and dimer **22** 171 mg (41%) was obtained as a yellow powder, mp >260°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 1.0 (s, 18H, *t*-Bu), 7.27 (s, 2H, NH), 7.9 (m, 8H, H_{5-8}); ir: ν 3400, 3120, 2967, 1718, 1676, 1508, 1472 cm^{-1}.

Anal. Calcd. for $C_{26}H_{28}N_6O_2$ (M = 456.6): C, 68.42; N, 18.42; H, 6.14. Found: C, 68.49; N, 18.05; H, 6.43.

2-Iodo-3-pivaloylaminoquinoxaline (**20**).

Metalation of **3** (438.0 mg, 1.91 mmoles) with lithium 2,2,6,6-tetramethylpiperidide (7.64 mmoles) according to the general procedure, t_1 = 2 hours, and reaction with iodine (1.95 g, 7.64 mmoles), t_2 = 2 hours, afforded after chromatography with a 9/1 then 8/2 mixture of dichloromethane and ethylacetate, 61.3 mg (14%) of **3** recovered and 387.3 mg (57%) of **20** as yellow crystals, mp 99°; ^{1}H nmr (deuteriochloroform): δ 1.38 (s, 9H, *t*-Bu), 7.50 (m, 2H, H_6 + H_7), 7.89 (d, 1H, H_5), 8.02 (d, 1H, H_8), 8.53 (s, 1H, NH); ir: ν 3453, 3146, 2970, 1664, 1516, 1482, 1394, 1349 cm^{-1}.

Anal. Calcd. for $C_{13}H_{14}N_3OI$ (M = 355.2): C, 43.92; N, 11.82; H, 3.84. Found: C, 44.02; N, 11.58; H, 4.17.

3-Pivaloylaminoquinoxaline-2-carboxylic Acid (**21**).

Metalation of **3** (1.11 g, 4.84 mmoles) with lithium 2,2,6,6-tetramethylpiperidide (19.36 mmoles) according to the general procedure, t_1 = 2.5 hours, and reaction with solid carbon dioxyde in excess, t_2 1.5 hours, afforded after filtration and drying in an oven 423.1 mg (32%) of a pale yellow solid **21**, mp 107°; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.24 (s, 9H, *t*-Bu), 8.11 (s, 1H, NH), 7.9 (m, 4H, H_{5-8}), 10.86 (s, 1H, COOH); ir: ν 3406, 3240, 2972, 1703, 1576, 1513, 1472, 1159 cm^{-1}.

Anal. Calcd. for $C_{14}H_{15}N_3O_3$, H_2O (M = 291.3): C, 57.67; N, 14.41; H, 5.83. Found: C, 56.90; N, 14.12; H, 5.75.

REFERENCES AND NOTES

[1] A. Turck, N. Plé, L. Mojovic and G. Quéguiner, *Synthesis*, 881 (1988).

[2] A. Turck, N. Plé, L. Mojovic and G. Quéguiner, *J. Heterocyclic Chem.*, **27**, 1377 (1990).

[3] N. Plé, A. Turck, E. Fiquet and G. Quéguiner, *J. Heterocyclic Chem.*, **28**, 283 (1991).

[4] A. Turck, D. Trohay, L. Mojovic and G. Quéguiner, *J. Organomet. Chem.*, **412**, 301 (1991).

[5] N. Plé, A. Turck, F. Bardin and G. Quéguiner, *J. Heterocyclic Chem.*, **29**, 467 (1992).

[6] A. Turck, N. Plé, D. Trohay, B. Ndzi and G. Quéguiner, *J. Heterocyclic Chem.*, **29**, 699 (1992).

[7] A. Turck, N. Plé, B. Ndzi, G. Quéguiner, N. Haider, H. Schullet and G. Heinisch, *Tetrahedron*, **49**, 599 (1993).

[8] N. Plé, A. Turck, P. Martin, S. Barbey and Quéguiner, *Tetrahedron Letters*, **34**, 1605 (1993).

[9] G. W. H. Cheeseman and R. F. Cookson, *Chem. Heterocyclic Compd.*, **35**, 1 (1979).

[10] J. S. Ward and L. Merritt, *J. Heterocyclic Chem.*, **28**, 765 (1991).

[11] F. S. Wolf (to Merck and Co) US Patent, 2,573,870; *Chem. Abstr.*, **45**, 4274 (1951).