The Preparations of Some Substituted Quinoxalines and 1,2,3,4-Tetrahydroquinoxalines

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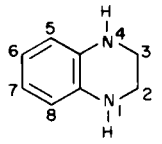
Current interest in the preparations of substituted 1,2,3,4-tetrahydroquinoxalines (**1**) (1), prompts us to report our results in this area. In general, quinoxalines



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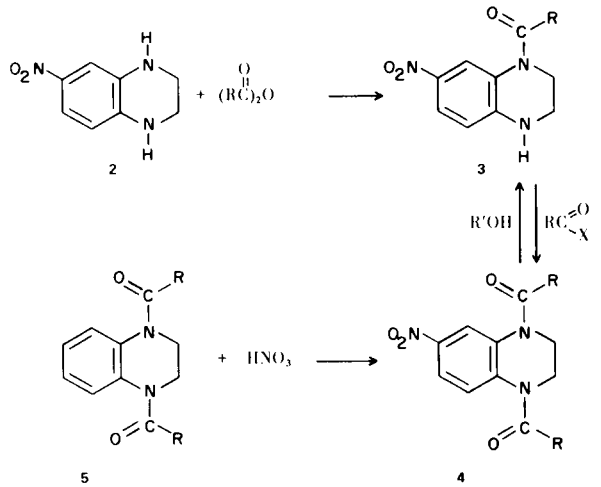
can be reduced by catalytic hydrogenation or by lithium aluminum hydride giving the corresponding 1,2,3,4-tetrahydroquinoxalines (2). As starting materials, several of the quinoxalines of Table I were prepared by the method of Cavagnol and Wiselogle (3) and reduced catalytically.

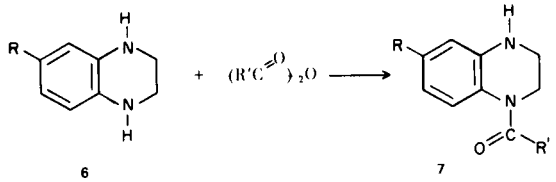
It was also found that 6-methylquinoxaline could be selectively brominated with *N*-bromosuccinimide to the new 6-bromomethylquinoxaline. The intermediate could be utilized to introduce a variety of nonconjugating substituents on the benzo ring. One such example was the preparation of 6-morpholinomethylquinoxaline.

It was found convenient in cases of certain sensitive tetrahydroquinoxalines (*i.e.*, 6-methoxytetrahydroquinoxaline) to isolate them as the trifluoroacetates. The parent compounds could be readily regenerated *in situ* by mild alkaline hydrolysis. There was no difficulty in preparing the bisacylated derivatives except in cases such as 6-nitrotetrahydroquinoxaline which was very slow owing to the electron-withdrawing effect of the nitro group on the *p*-amino substituent (4).



(a) R = Me
(b) R = CF_3

The electronic effects of various substituents in the 6-position of tetrahydroquinoxaline are pronounced enough to allow selective monoacylation (5). Thus, 6-nitrotetrahydroquinoxaline was monoacylated with acetic anhydride or trifluoroacetic anhydride exclusively at the 4-position (**2** → **3**). The position of acylation was demonstrated unambiguously by observation of the downfield shift of the signal due to the 5-position proton from δ 7.55 in **2** to δ 8.50 in **3a** and δ 8.74 ppm in **3b**. Conversely, electron-donating substituents as in **6** gave exclusive acylation at the 1-position resulting in the derivatives **7**, as evidenced by no significant chemical shift of the signal for the proton at position 5. The bisacylated products all showed a downfield shift of the 5-position proton of 1.0 to 1.4 ppm.



6

(a) R = Me
(b) R = Cl

7

(a) R = Me, R' = Me
(b) R = Cl, R' = Me
(c) R = Me, R' = CF_3
(d) R = Cl, R' = CF_3

In the course of these studies, it was found much more convenient to prepare **2**, **3**, and **4** by nitration of **5** (see Experimental). This circumvents the former tedious preparation of **2** (6) and is complementary to the newer reductive procedure (1).

EXPERIMENTAL

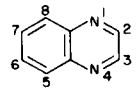
All analyses are reported in Tables I and II.

6-Bromomethylquinoxaline.

A mixture of 1.44 g. (0.01 mole) of 6-methylquinoxaline (3), 1.80 g. (0.01+ mole) of *N*-bromosuccinimide (kept over phos-

TABLE I

New Substituted Quinoxalines



Substituents	Method of Prep.	Yield %	M.p./B.p. (purification)	Analyses (Calcd./Found) C	H	Br	F	N
6-Trifluoromethyl	A	43.3	m. 78° (sublimed)	54.6	2.5		28.8	14.2
				55.0	2.8		28.6	13.9
6-Methoxycarbonyl	A	46.0	m. 100° (ligroine)	63.9	4.3			14.9
				64.1	4.6			15.1
6-Bromomethyl	B	90.0	m. 100-105° (sublimed)	48.5	3.2	35.8		12.6
				48.2	3.3	35.9		13.0
6-Morpholinomethyl	B	18.0	b. 0.1 mm. 135-145°					18.3
								18.0
5,8-Dimethoxy	A	6.0	m. 152°	63.2	5.3			14.7
				63.0	5.4			14.9
6,7-Methylenedioxy	A	12.3	m. 156°	62.1	3.5			16.1
				62.0	3.3			16.2

A. = By the method of Reference 4. B. = See the experimental section.

phorus pentoxide *in vacuo* 4 hours), 20 ml. of carbon tetrachloride, and 100 mg. of azobisisobutyronitrile was heated at reflux 3.5 hours (72 percent complete by nmr). The colorless liquid was decanted from the black, insoluble residue and concentrated at reduced pressure yielding 2.00 g. (90% of theoretical) of crude product, m.p. 85-97°, which could be used without further purification. Purified material was obtained with considerable loss in yield by repeated crystallizations from ligroine and sublimation at 70°/1 mm, m.p. 100-105° dec. This product is unstable and cannot be stored. The nmr spectrum of a carbon tetrachloride solution showed absorptions at δ 4.66 (S), (-CH_2Br), δ 7.96 (M) (Ar-H_3), and δ 8.79 (S) ppm (heteroaromatic -H_2).

6-Morpholinomethylquinoxaline.

To a mixture of 2.8 g. (0.031 mole) of morpholine, 10 g. anhydrous potassium carbonate, and 50 ml. of 1,2-dimethoxyethane (DME) was added 7.2 g. (0.032 mole) of 6-bromomethylquinoxaline in 50 ml. of DME during one hour. The mixture was stirred an additional 4 hours, filtered, and distilled. The fraction boiling at 135-145°/0.1 mm, 1.33 g. (18% of theoretical), showed nmr absorptions in deuteriochloroform at δ 2.51 and δ 3.75 (M) (morpholino), δ 3.75 (S) (CH_2-N≺), δ 7.98 (M) (Ar-H_3), and δ 8.78 ppm (heteroaromatic -H_2).

1,4-Bistrifluoroacetyl-6-methoxy-1,2,3,4-tetrahydroquinoxaline. (Representative of General Method for Table II).

A mixture of 32 g. (0.2 mole) of 6-methoxyquinoxaline (3), 250 ml. of benzene, and 1 g. of platinum oxide was hydrogenated at 59 psi initial pressure and ambient temperature to 0.4 mole uptake of hydrogen. The solution was filtered, concentrated under vacuum, and the crystalline residue (33.8 g., m.p. 73-77°) was added to 75 ml. of trifluoroacetic anhydride at 0 to 5°, stirred overnight (20 hours) at room temperature, poured into methanol-ice, stirred, filtered, and recrystallized from methanol/water, yielding 42.6 g. (57% of theoretical), m.p. 110-110.5°. The nmr spectrum of a deuteriochloroform solution had absorptions at δ 3.82 (S) (CH_3O-), δ 4.08 (S) (≻NCH_2CH_2N≺), and δ 6.71 to 7.13 ppm (M) (Ar-H_3).

7-Nitro-1-trifluoroacetyl-1,2,3,4-tetrahydroquinoxaline.

A. General Monoacylation Procedure (5).

A suspension of 8.96 g. (0.05 mole) of 6-nitro-1,2,3,4-tetrahydroquinoxaline in 100 ml. of chloroform was treated gradually with 11.55 g. (0.05 mole) of trifluoroacetic anhydride at 27-30°. Addition required ~10 minutes, with some cooling. The mixture was stirred an additional 2 hours at room temperature, filtered, and washed with chloroform yielding 13.0 g. (94.7% of theoretical), m.p. 135-145°. Recrystallization from methanol raised the melting point to 182.5-183.5°. Nmr absorption of a DMSO-d_6 solution appeared at δ 3.70 (CH_2 at C-2), δ 4.0 (CH_2 at C-3), δ 6.97 (D) ($J_{8,7}$ = 9.0 Hz, C-8), δ 8.16 (Q) ($J_{7,8}$ = 9.0 Hz, $J_{7,5}$ = 2.4 Hz, C-7), δ 8.74 ppm (M) (C-5).

B. Nitration of Bistrifluoroacetyltetrahydroquinoxaline.

To 100 ml. of nitric acid (sp. g. = 1.59) at 0 to 5° was added gradually 27.7 g. (0.085 mole) of 1,4-bistrifluoroacetyl-1,2,3,4-tetrahydroquinoxaline. The mixture was stirred an additional 10 minutes, poured into ice/water, filtered, and washed with cold water yielding 39.0 g., m.p. 118-120°. Recrystallization from isopropyl alcohol gave 15.5 g. (49% of theoretical) of 1,4-bistrifluoroacetyl-6-nitro-1,2,3,4-tetrahydroquinoxaline, m.p. 120-121°.

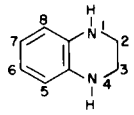
Recrystallization from methanol/water converted this product to 7-nitro-1-trifluoroacetyl-1,2,3,4-tetrahydroquinoxaline (95% of theoretical), m.p. 182.5-183.5°.

1,1-Dimethyl-1,2,3,4-tetrahydroquinoxalinium *p*-Toluenesulfonate.

A mixture of 7.4 g. (0.05 mole) of 1-methyl-1,2,3,4-tetrahydroquinoxaline (3) and 9.3 g. (0.05 mole) of methyl *p*-toluenesulfonate was prepared and allowed to stand at room temperature. A slight exotherm occurred and the mixture formed a glass

TABLE II

New Substituted 1,2,3,4-Tetrahydroquinoxalines



Substituents	Method	Yield %	M.p., °C (purification)	Analyses (Calcd./Found) C	H	Cl	F	N	S
1,4-Bistrifluoroacetyl	A	87.5	118.0-(CH_3OH/H_2O)	44.2	2.5		34.9	8.6	
			118.5	44.2	2.5		35.2	8.8	
1,1-Dimethyl *p*-toluenesulfonate salt	B	8.1	153-155 (CH_3CN)	61.1	6.6			8.4	
				61.3	6.8			8.7	
1-Acetyl-6-methyl	A	79.7	71-73 (Benzene/ ligroine)	69.5	7.4				14.8
				69.3	7.5				14.6
1-Acetyl-6-chloro	A	91.2	80-90 (Benzene/ ligroine)	57.1	5.3	16.9			13.3
				57.4	5.3	16.8			13.4
1,4-Bis(trifluoro-acetyl)-6-methoxy	A	57.0	110.0-(CH_3OH/H_2O)	43.8	2.8		32.0		7.9
			110.5	43.7	2.8		32.4		8.2
1-Acetyl-7-nitro	A	39.3	204-205 (CH_3OH)	54.3	5.0			19.0	
				54.4	5.1			18.9	
1-Trifluoroacetyl-7-nitro	B	94.7	182.5-(CH_3OH)	43.7	2.9		20.7	15.3	
			183.5	43.5	2.8		20.4	15.3	
1,4-Bis(trifluoro-acetyl)-7-nitro	B	74.7	120-121 (i-C_3H_7OH)	38.9	1.9		30.7	11.3	
				39.2	2.3		30.8	11.4	
1,4-Bis(acetyl)-7-nitro	A	100	Oil	54.7	5.0				
				54.6	5.2				
1-Benzyloxycarbonyl	A	31.4	117-118 (C_2H_5OH)	72.2	6.1				
				72.3	5.9				
6,7-Dimethyl	A	69.0	154 (Benzene)	74.2	8.7			17.3	
				74.4	8.3			17.5	
6,7-Dimethyl-1,4-bis(trifluoroacetyl)	A	75.8	84 and 103 (CH_3OH/H_2O)	47.3	3.9		32.0	7.9	
				47.1	3.7		31.9	7.5	
6-Methyl-1,4-bis(trifluoroacetyl)	A	94.3	98-99 (CH_3OH/H_2O)	45.9	3.0		33.5	8.2	
				45.7	3.1		33.2	8.4	
6-Carboxylic acid hydrochloride	A	46.8	204-230 dec. (conc. HCl)	50.4	5.2	16.6		13.1	
				50.5	5.2	16.7		13.0	
6-Trifluoromethyl	A	66.8	126-127 (sublimed)	53.5	4.5		28.2	13.9	
			(lit. (1), 123-124)	53.5	4.5		28.3	14.2	

Method "A" - See experimental for general method. Method "B" - See experimental for specific method.

within 15 minutes. The mixture was dissolved in methanol, precipitated with ether, filtered (sticky mass), and recrystallized from acetonitrile 2 times yielding 0.6 g. (8.1% of theoretical), m.p. 153-155°. The nmr spectrum of a DMSO-d_6 solution showed absorptions at δ 2.33 (S) (CH_3 on PTS^-), δ 7.45 (Q) (Ar-H_4 of PTS^-), δ 3.00 (M) (-CH_2CH_2-), δ 3.53 (M) ($(CH_3)_2N^+$ <), and δ 6.60-7.95 ppm (M) (Ar-H_4).

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