New Synthetic Routes to the Potent Mutagen 3,7,8-Trimethyl-3*H*-imidazo[4,5-*f*]quinoxalin-2-amine

Kjell Olsson and Spiros Grivas

Department of Chemistry and Molecular Biology, Swedish University of Agricultural Sciences, P.O. Box 7016, S-750 07 Uppsala, Sweden

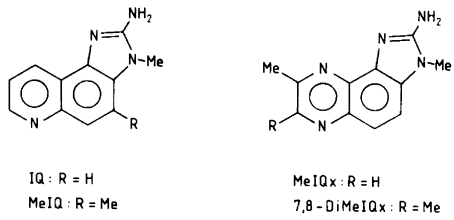
Olsson, Kjell and Grivas, Spiros, 1986. New Synthetic Routes to the Potent Mutagen 3,7,8-Trimethyl-3*H*-imidazo[4,5-*f*]quinoxalin-2-amine. – Acta Chem. Scand. B 40: 486–492.

The title compound (7,8-DiMeIQx) has been prepared in two operations from *N*,2,3-trimethyl-6-quinoxalinamine (*1*) or from 2,3-dimethyl-6-nitro-5-quinoxalinamine (*3*). Alternative syntheses of *1* have been investigated. The choices among the various routes to 7,8-DiMeIQx via *1* or *3* are discussed.

We have previously reported convenient large scale syntheses of highly mutagenic imidazoquinolin- and imidazoquinoxalin-2-amines.[1–3] Some of these heterocyclic amines (the so-called IQ compounds; Scheme 1) have been found in fried beef, beef extracts and broiled fish.[4,5] They are also formed in model reaction systems (hexose, amino acid and creatinine) in very low yields.[6,7] It has been postulated that the IQ compounds are formed from Maillard reaction products, e.g., 2-methylpyridine or 2,5-dimethylpyrazine, and creatin(in)e.[8]

Like many other mutagens, the IQ compounds require metabolic activation by enzymes in order to be active in the *Salmonella*/mammalian microsome mutagenicity test system (Ames test).[9] During this activation, hydroxylation of the 2-amino group occurs.[10] It has been suggested that the ultimate forms of IQ, MeIQ and MeIQx in *Salmonella* are sulfate esters of their N^2-hydroxy derivatives.[11] The interested reader is referred to recent reviews[4] for more information on the toxicity, metabolism and studies on the binding of these substances to DNA.[12]

The carcinogenicity of the IQ compounds is now being investigated in long term animal studies by Sugimura's group in Japan. High incidences of tumours in the liver, forestomach, lung, skin and oral cavity have been observed in rats and mice when IQ and/or MeIQ was incorporated in their diet.[5,13]



Scheme 1.

The significance of the relation between the mutagen formation and cooking conditions common in the household is obvious. As expressed by Felton *et al.*,[14] only when the mechanism of action of these mutagens, their metabolism, their mutagenicity and their carcinogenicity have been determined, can valid risk assessment begin. Thus, synthetic routes to produce these compounds are required in order to (i) confirm their presence in complex mixtures (ii) investigate their formation mechanisms and (iii) provide a source for animal bioassay and toxicological tests.

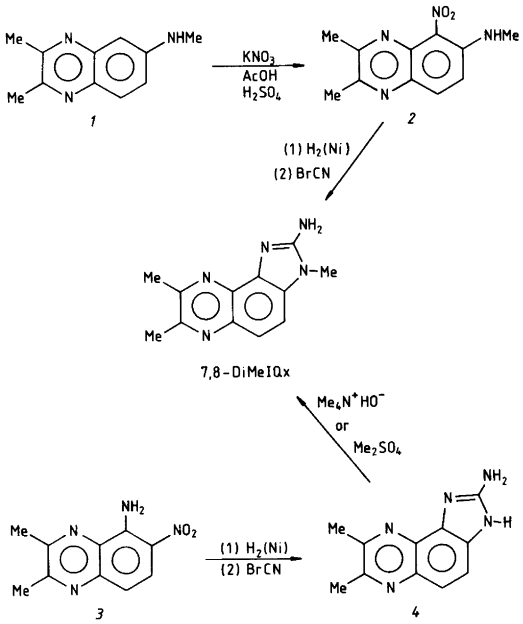
The synthesis of 7,8-DiMeIQx on a micro scale has been achieved by radical methylation of MeIQx by *t*-butyl hydroperoxide and iron(II) sulfate in aqueous acid.[6] In this paper, we report some convenient large scale syntheses of the title compound, which was recently identified in a heated model mixture.[6]

Results

By analogy with previous work[2,3] an attractive intermediate was the known[15] *N*,2,3-trimethyl-6-quinoxalinamine (*1*; see Scheme 2). This was nitrated and the product (*2*) hydrogenated. The resulting diamine was not isolated but converted directly to the title compound (7,8-DiMeIQx) by reaction with cyanogen bromide.

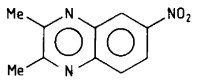
The nitration of quinoxalines is rather difficult and touchy[3,16] in contrast to that of quinolines.[1] Therefore, another route was tried, starting with the hydrogenation of the known[17] 2,3-dimethyl-6-nitro-5-quinoxalinamine (*3*). Again, the resulting diamine[17] was not isolated but converted directly to the imidazoquinoxaline *4* with cyanogen bromide. Methylation of *4* to afford the title compound was achieved by two methods, though both proceeded in low yields. By one method reported by German scientists (using Me_2SO_4 and $NaHCO_3$),[18] compound *4* was converted to 7,8-DiMeIQx in only 9 % yield. Alternatively, by heating a mixture of *4* and tetramethylammonium hydroxide under reduced pressure,[19] the title compound was isolated in 17 % yield. The latter method is practical only when small quantities of 7,8-DiMeIQx are required.

Whereas *3* was readily available[17] in high yield

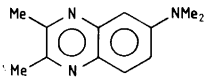


1 2 3 4

Scheme 2.



5



6

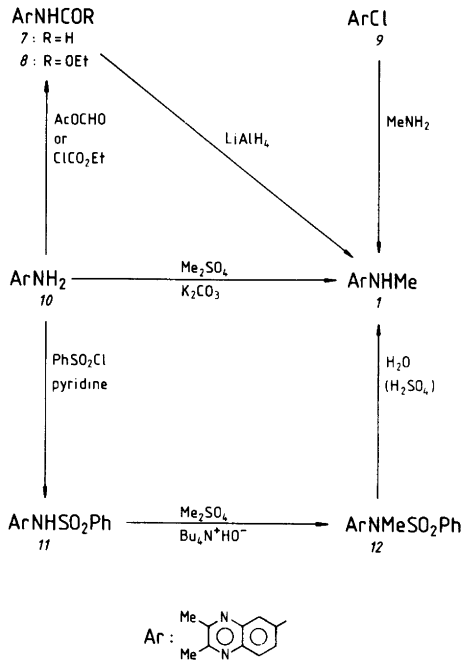
from 2,3-dimethyl-6-nitroquinoxaline (*5*),[20] the synthesis of *1* presented difficulties. According to the only method found in the literature,[15] compound *1* is prepared by methylation of 2,3-dimethyl-6-quinoxalinamine (*10*; Scheme 3) with dimethyl sulfate. In our hands, this method invariably produced a mixture of the amines *1*, *6* and *10*, from which *10* was isolated in <25 % yield by column chromatography. Similar results were obtained when the methylation was performed in refluxing acetone in the presence of potassium carbonate. When iodomethane was used as methylating agent, most of the starting material was intact even after 24 h reaction at reflux temperature. Alternative routes to *1* were therefore investigated (see Scheme 3).

Compound *1* can be obtained by direct replacement of the chlorine atom of *9* by a methylamino group in a steel autoclave.[2,3] However, when large amounts (50–60 g) of *1* are required, the direct replacement of the halogen by the methylamino group is not the most practical. This would require a very big steel autoclave or repetitive operations. Attempts to use compound *5* instead of *9* were unsuccessful. Thus, alternative routes were tried. By analogy with previous work,[21] compound *10* was formylated and formamide *7* reduced to *1*. Alternatively, *10* was converted to the carbamate *8* and this subsequently reduced to *1*.[22] A third route employed was to treat *10* with benzenesulfonyl chloride, methylate the resulting sulfonamide *11* and finally hydrolyse the product *12* to *1*.

Discussion

Among the four routes from *10* to *1* shown in Scheme 3, the direct route was the least convenient one because of the low yield (≤28 %) and the necessary separation of *1* from *10* and *6*. The three indirect routes are about equally satisfactory. The overall yields via *7* (58 %) and *8* (60 %) were practically the same. The solubility of *8* in tetrahydrofuran was better than that of *7*; in large scale reductions to *1*, the carbamate route is to be preferred. The route via *11* and *12* was longer

and the overall yield (50%) slightly poorer, but this was compensated for by the possibility of carrying out the sequence *12*→*1*→*2* in one operation without isolation of *1*.



Scheme 3.

Whereas *10* is advantageously[23] prepared via *5* from commercial 4-nitro-*o*-phenylenediamine, *9* may be obtained directly from commercial 4-chloro-*o*-phenylenediamine. For small or medium scale synthesis of *1*, we therefore preferred the simple route *9*→*1*, which proceeded in 63% yield, to all the routes from *10*. (The yield of *1* from the fluoro analogue of *9* would probably be even higher, but the extra effort to prepare 4-fluoro-*o*-phenylenediamine[2] is hardly worthwhile.) Thus, the overall yield of *1* was 49% from 4-chloro-*o*-phenylenediamine (two steps via *9*) but ≤45% from 4-nitro-*o*-phenylenediamine (≥4 steps via *5*, *10* and, e.g., *8*).

As for the two main routes to the title compound shown in Scheme 2, the otherwise attractive route from *3* is disqualified until an efficient and selective method for methylation of *4* is found. The overall yield is only 12% from *3* and 7% from 4-nitro-*o*-phenylenediamine (4 operations via *5*, *3* and *4*). On a large scale, the yields are even poorer, since *4* has to be methylated with dimethyl sulfate. On the other hand, the overall yield of 7,8-DiMeIQx is 39% from *1*, 19% from 4-chloro-*o*-phenylenediamine (4 operations via *9*, *1* and *2*). Clearly, the route via *1* is superior.

Finally, no attempts were made to synthesize the title compound by radical methylation of MeIQx,[6] since methods to prepare MeIQx, reported previously[2,24] or analogous to those suggested here for 7,8-DiMeIQx, involve the separation of an isomeric mixture. This originates from the classical condensation of pyruvaldehyde with a 4-substituted *o*-phenylenediamine derivative. It is therefore unlikely that MeIQx will be more readily available than the title compound.

Experimental

All reactions and purifications were monitored by TLC on aluminum sheets coated with silica gel 60 F_{254} (Merck) or by GLC on a 25 m × 0.24 mm i.d. capillary column coated with CP Sil 5 and heated from 130 to 265 °C at 6 °C/min. UV irradiation was used to detect TLC spots. Column chromatography at atmospheric pressure and flash liquid chromatography[25] (FC) was performed on silica gel (230–400 mesh ASTM, Merck). Evaporations were performed at reduced pressure below 40 °C. The organic solvents were freshly distilled. Melting points were corrected. The mass spectra (70 eV, direct insertion) were obtained on a Finnigan 4021 instrument with electron impact ionization and an ion source temperature of 200 °C. The ^{1}H NMR spectra were recorded on a Jeol FX 90 Q (89.55 MHz) instrument at 29 °C, unless otherwise stated.

Materials

Compounds *3*,[17] *5*,[26,17] *9*,[26,27] and *10*[20] were obtained according to, or in analogy with, the respective references first cited. The following spectral data have apparently not been reported.

Compound 3. MS, *m/z* (rel. int.): 218 (100, M), 172 (47), 42 (45), 43 (36), 63 (28), 188 (23). ^{1}H NMR ($CDCl_3$): δ 2.74 (2- and 3-Me, s), 7.13 (8-H, d), 7.80 (NH_2, broad s), 8.28 (7-H, d); $|J|$ 9.8 (7,8) Hz.

Compound 5. MS, *m/z* (rel. int.): 203 (100, M), 162 (98), 75 (91), 116 (89), 74 (25), 78 (24).

^{1}H NMR ($CDCl_3$): δ 2.79 (2- and 3-Me, s), 8.10 (8-H, d), 8.45 (7-H, dd), 8.90 (5-H, d); |*J*| 0.4 (5,8), 2.4 (5,7), 9.3 (7,8) Hz.

Compound 9. MS, *m/z* (rel. int.): 151 (100), 192 (78, M), 149 (31), 110 (31), 153 (30), 111 (14). ^{1}H NMR ($CDCl_3$): δ 2.72 (2- and 3-Me, s), 7.59 (7-H, dd), 7.89 (8-H, dd), 7.95 (5-H, dd); |*J*| 0.4 (5,8), 2.2 (5,7), 8.9 (7,8) Hz.

Compound 10. MS, *m/z* (rel. int.): 91 (100), 173 (88, M), 42 (36), 63 (34), 64 (21), 132 (20). ^{1}H NMR ($CDCl_3$): δ 2.65 (2- and 3-Me, s), 4.08 (NH_2, broad s), 7.07 (5-H, d), 7.08 (7-H, dd), 7.76 (8-H, d); |*J*| 2.8 (5,7), 9.3 (7,8) Hz.

Syntheses of the title compound (Scheme 2)

N,2,3-Trimethyl-5-nitro-6-quinoxalinamine (2). *A.* Compound *1* (1.75 g, 9.35 mmol) was dissolved in glacial acetic acid (20 ml). Cold concentrated sulfuric acid (15 ml) was added dropwise to the solution, so that the reaction mixture temperature did not exceed 25 °C (ice bath). When all sulfuric acid had been added, the solution was cooled to 5–10 °C and powdered potassium nitrate (975 mg, 9.75 mmol) was added in one portion. The reaction was complete after 2 h stirring at 20 °C (TLC, CH_2Cl_2/EtOAc, 4:1 v/v). The mixture was poured onto ice, neutralized with NH_3 and extracted with $CHCl_3$. The organic phase was separated, washed with water, dried and evaporated to dryness. Column chromatography (FC, CH_2Cl_2/MeOH/NH_3; 80:1:1) and recrystallization from ethyl acetate yielded 1.17 g (54 %) of pure *2*. M.p. 190–191.5 °C. Anal. $C_{11}H_{12}N_4O_2$: C,H,N. MS, *m/z* (rel. int.): 232 (100, M), 132 (50), 171 (36), 157 (36), 75 (34), 77 (33). ^{1}H NMR ($CDCl_3$): δ 2.65 (2- or 3-Me, s), 2.71 (3- or 2-Me, s), 3.13 (NMe, d), 7.26 (7-H, d), 7.3 (NH, broad s), 7.95 (8-H, d); |*J*| 5.1 (*N,N*), 9.4 (7,8) Hz.

B. A large water bath was kept at 45–55 °C. Concentrated sulfuric acid (180 ml) was stirred vigorously in a large beaker, cooled in much ice-water. A solution or slurry of *12* (Scheme 3, 31.3 g, 100 mmol) in glacial acetic acid (150 ml) was added at such a rate that the temperature rose to and remained at 45–55 °C. The beaker was immediately transferred to the water bath. After stirring for 15–20 min at the same temperature, the beaker was returned to the ice-water and the stirring continued. When the temperature reached 10 °C, powdered potassium nitrate (10.6 g, 105 mmol) was added in one portion. After stirring for 2 h at 20 °C, the reaction mixture was processed as in method *A*. Yield 37 % (8.2 g).

7,8-Dimethyl-3H-imidazo[4,5-f]quinoxalin-2-amine (4) was prepared from *3* as described below for *2* → 7,8-DiMeIQx. The yield was 71 %. M.p. >300 °C. Anal. $C_{11}H_{11}N_5$: C,H,N. MS, *m/z* (rel. int.): 213 (100, M), 131 (44), 42 (21), 43 (10), 214 (7), 77 (5), 44 (5), 104 (4), 103 (4), 76 (2). ^{1}H NMR (pyridine-d_5): δ 2.55 (7- or 8-Me, s), 2.61 (8- or 7-Me, s), 6.5 (NH and NH_2, broad s), 7.99 (4- or 5-H, d), 8.04 (5- or 4-H, d); |*J*| 8.8 (4,5) Hz.

3,7,8-Trimethyl-3H-imidazo[4,5-f]quinoxalin-2-amine (7,8-DiMeIQx). It has been shown that the N-methyl group and the imidazo moiety of the IQ compounds are necessary for their toxicity.[28] *Thus contact with the reaction mixtures or the product in the final steps (2 → 7,8-DiMeIQx and 4 → 7,8-DiMeIQx) should be avoided.*

A. A mixture of *2* (650 mg, 2.80 mmol), Raney nickel (one teaspoon) and absolute ethanol (145 ml) was hydrogenated with vigorous stirring under ambient conditions. TLC monitoring (CH_2Cl_2/EtOAc, 2:1 v/v) indicated completion of the reaction after 40–45 min. The catalyst was filtered through a no. 3 sintered filter and filter aid, and the filtrate concentrated to 65 ml. Cyanogen bromide (327 mg, 3.09 mmol) was dissolved in the filtrate and the reaction mixture allowed to stand at 20 °C. TLC monitoring (CH_2Cl_2/MeOH, 4:1 v/v) showed completion of the reaction after 3.5 h. The reaction mixture was left at 0 °C overnight. The hydrobromide of 7,8-DiMeIQx was collected, washed with cold chloroform and dissolved in 50 % aq. methanol. The solution was treated with conc. ammonia and evaporated to dryness. FC (CH_2Cl_2/MeOH, 4:1 v/v) of the residue yielded 450 mg (72 %) of pure 7,8-DiMeIQx. M.p. >300 °C. Anal. $C_{12}H_{13}N_5$: C,H,N. MS, *m/z* (rel. int.) 227 (100, M), 145 (60), 226 (57), 42 (54), 57 (53), 71 (31). ^{1}H NMR ($(CD_3)_2SO$): δ 2.63 (7- or 8-Me, s), 2.67 (8- or 7-Me, s), 3.64 (3-Me, s), 6.5 (NH_2, broad s), 7.46 (4- or 5-H, d), 7.67 (5- or 4-H, d); |*J*| 8.7 (4,5) Hz.

B. (cf. Ref. 18) A mixture of *4* (147 mg, 0.69 mmol), sodium hydrogen carbonate (70 mg, 0.83 mmol) and dimethyl sulfate (87 mg, 0.69 mmol) in water (12 ml) was left overnight at 25 °C. Column chromatography on silica gel at atmospheric pressure (CH_2Cl_2/MeOH, 4:1 v/v) yielded 7,8-DiMeIQx (14 mg, 9 %). Higher temperatures and longer reaction time gave no better results.

C. A mixture of *4* (132 mg; 0.62 mmol) tetramethylammonium hydroxide pentahydrate (112.5 mg, 0.62 mmol) and water (5 ml) was heated together in a sublimation apparatus under oil pump vacuum to ~200 °C. The sublimate collected on the cold finger was chromatographed on silica gel at atmospheric pressure (CH_2Cl_2/MeOH, 4:1 v/v). The title compound was isolated in 17 % yield (24 mg) (cf. Ref. 19).

Syntheses of compound 1 (Scheme 3)

Five methods (*A–E*) are described for the synthesis of N,*2,3-trimethyl-6-quinoxalinamine* (*1*). The methods gave identical (GLC, TLC) products.

A. Compound *1* was prepared from *9* and methylamine as described previously for the similar reaction of 6- and 7-fluoro-2-methylquinoxaline,[2] with the following modifications: 26 h at 200 °C, FC solvent system CH_2Cl_2/EtOAc, 3:2 v/v. Recrystallization from petroleum ether (b.p. 60–70 °C) yielded pure *1* (63 %), m.p. 122.5–123.5 °C (lit.[15] 134 °C). Anal. $C_{11}H_{13}N_3$: C,H,N. MS, *m/z* (rel. int.): 187 (100, M), 105 (74), 186 (41), 63 (19), 55 (17), 188 (15). ^{1}H NMR ($CDCl_3$): δ 2.65 (2- or 3-Me, s), 2.66 (3- or 2-Me, s), 2.95 (NMe, d), 4.2 (NH, broad s), 6.89 (5-H, d), 7.02 (7-H, dd), 7.72 (8-H, d); |*J*| 2.6 (5,7), 5.2 (*N,N*), 8.8 (7,8) Hz.

B. A cold (0–5 °C) solution of *7* (1.06 g, 5.25 mmol) in dry tetrahydrofuran (50 ml) was added cautiously to a cold solution of lithium aluminum hydride (0.36 g, 9.5 mmol) in dry tetrahydrofuran (25 ml). The reaction mixture was stirred at 0–5 °C. TLC monitoring showed completion of the reaction after ~4 h ($MeCN/CH_2Cl_2$, 5:2 v/v). Ethyl acetate (10 ml) was added to the mixture in order to decompose the excess of hydride. The reaction mixture was poured gradually into an excess of ice cold 0.25 M sulfuric acid to dissolve the precipitated aluminum compounds. The organic solvents were removed. The remaining suspension was treated with a little water, neutralized with ammonia and extracted with $CHCl_3$. The extract was washed with water and evaporated to dryness. Crystallization from petroleum ether (b.p. 60–70 °C) gave 0.73 g (74 %) of *1*, m.p. 122–123 °C.

C. Reduction of *8* was performed as described for *7* in method *B*, or alternatively by using a Soxhlet apparatus (containing the substrate *7* or *8*) inserted between the reaction flask (containing a suspension of lithium aluminum hydride in tetrahydrofuran) and the reflux condenser. Methods *B* and *C* gave identical products and similar yields of *1*.

It should be noted that the higher the reaction temperature, the shorter the reaction time but the lower the yield of these reductions.

D. A mixture of *12* (0.6 g, 1.8 mmol) and conc. sulfuric acid (5 ml) was heated for 25 min on a steam bath. TLC monitoring of the reaction: CH_2Cl_2/MeCN, 4:1 v/v. The reaction mixture was poured onto ice and made alkaline (pH 8) with ammonia. Extraction with $CHCl_3$, FC (CH_2Cl_2/MeCN, 6:1 v/v) of the extract and recrystallization from petroleum ether (b.p. 60–70 °C) yielded 0.24 g (69 %) of *1*.

E. Exploratory experiments to obtain *1* directly from *10* were performed, and followed by GLC. In general, *10* was dissolved in acetone or acetonitrile and refluxed with different amounts of potassium carbonate and dimethyl sulfate or iodomethane. The optimum conditions found were the following: *10* (1 equiv.) was refluxed in acetone for 7 h in the presence of potassium carbonate and dimethyl sulfate (1.5 equiv. of each). Under these conditions, ~28 % of *10*, 57 % of *1* and 15 % of *6* were present as determined by GLC. When longer reaction times or larger amounts of dimethyl sulfate were employed, *6* predominated. Thus, the reaction could be interrupted after 7 h and the unreacted starting material separated from the products by, e.g., FC (CH_2Cl_2/EtOAc, 1:1 v/v).

N,N,*2,3-Tetramethyl-6-quinoxalinamine* (*6*) was obtained as a by-product, when *1* was prepared by method *E* (see above). M.p. 142–144 °C. Anal. $C_{12}H_{15}N_3$: C,H,N. MS, *m/z* (rel. int.) 201 (100, M), 200 (63), 42 (46), 69 (13), 202 (15), 119 (11). ^{1}H NMR ($CDCl_3$): δ 2.65 (2- or 3-Me, s), 2.66 (3- or 2-Me, s), 3.09 (NMe_2, s), 7.00 (5-H, d), 7.28 (7-H, dd), 7.81 (8-H, d); |*J*| 2.8 (5,7), 9.2 (7,8) Hz.

N-*Formyl-2,3-dimethyl-6-quinoxalinamine* (*7*). *(cf. Ref. 21).* To a solution of *10* (1.8 g, 10.4 mmol) in abolute formic acid (70 ml) a mixture of acetic anhydride (2.5 g) and absolute formic acid (25 ml) was added. The mixture was left for 75 min at room temperature when TLC monitoring ($MeCN/CH_2Cl_2$, 5:2 v/v) indicated completion of the reaction. The mixture was evaporated to dryness. The crude product was treated with a little water, made basic with aqueous NH_3 and extrac-

ted with $CHCl_3$. The extract was washed with water and evaporated to dryness. Recrystallization from EtOAc afforded 1.63 g (78%) of *7*, m.p. 211–213 °C. Anal. $C_{11}H_{11}N_3O$: C,H,N. MS, *m/z* (rel. int.) 201 (100, M), 91 (76), 63 (48), 119 (45), 41 (45), 57 (40). ^{1}H NMR ($(CD_3)_2SO$, 130 °C): δ 2.63 (2- and 3-Me, s), 7.72 (7-H, dd), 7.83 (8-H, dd), 8.05 (5-H, dd), 8.52 (CHO, d), 9.9 (NH, broad s); $|J|$ 0.6 (5,8), 2.1 (5,7), 4.3 (*N,N*), 9.0 (7,8) Hz.

Ethyl 2,3-dimethyl-6-quinoxalinecarbamate (8). Compound *10* (1.73 g, 10 mmol) was suspended in dry tetrahydrofuran (15 ml). Dry pyridine (0.9 ml, 11.2 mmol) was added to the suspension. Ethyl chloroformate (1.06 ml, 11 mmol) was added dropwise to the vigorously stirred mixture. Monitoring by TLC (CH_2Cl_2/MeCN, 4:1 v/v) indicated completion of the reaction 15 min afterwards. Cold water (30 ml) was added and the precipitated carbamate filtered off and washed with cold water (1.98 g, 81%). M.p. 169.5–171.5 °C. Anal. $C_{13}H_{15}N_3O_2$: C,H,N. MS, *m/z* (rel. int.) 245 (100, M), 63 (87), 173 (74), 186 (63), 172 (58), 42 (50). ^{1}H NMR ($CDCl_3$): δ 1.34 (Me, t), 2.70 (2- and 3-Me, s), 4.28 (CH_2, q), 6.98 (NH, broad s), 7.9–8.1 (5-, 7- and 8-H, m); $|J|$ 7.2 (Et) Hz.

N-*Benzenesulfonyl-2,3-dimethyl-6-quinoxalinamine (11).* Benzenesulfonyl chloride (4.4 g, 25 mmol) was added dropwise to a stirred and cooled solution of *10* (3.47 g, 20.0 mmol) in dry pyridine (15 ml, 185 mmol). The mixture was heated for 40 min on a steam bath when TLC monitoring (EtOAc/EtOH, 5:2 v/v) showed that the reaction was complete. The reaction mixture was poured onto ice (50 g) and 85% phosphoric acid (10 ml). The precipitate was collected and washed with ice cold water. Recrystallization from ethanol yielded 5.4 g (86%) of pure *11*, m.p. 239–240 °C. Anal. $C_{16}H_{15}N_3O_2S$: C,H,N. MS, *m/z* (rel. int.) 172 (100), 63 (77), 77 (73), 51 (44), 313 (25, M), 90 (20). ^{1}H NMR ($CDCl_3$, 50 °C): δ 2.67 (2- and 3-Me, s), 6.65 (NH, broad s), 7.4–7.9 (5-, 7-, 8-H and Ph, m).

N-*Benzenesulfonyl*-N,*2,3-trimethyl-6-quinoxalinamine (12).* Compound *11* (2.7 g, 8.6 mmol), dimethyl sulfate (1.14 g, 9.0 mmol) and tetrabutylammonium hydrogen sulfate (0.29 g, 0.86 mmol) were suspended in methylene chloride (10 ml). The mixture was stirred and refluxed with 2M NaOH (5 ml). TLC monitoring (CH_2Cl_2/MeCN, 4:1 v/v) indicated completion of the reaction after 50 min. The aqueous layer was separated and extracted once with $CHCl_3$. The methylene chloride layer was washed with water (2×6 ml). The organic phases were combined, dried and evaporated. The residue was recrystallized from ethanol and 2.37 g (84%) of pure *12* was obtained. M.p. 188–189 °C. Anal. $C_{17}H_{17}N_3O_2S$: C,H,N. MS, *m/z* (rel. int.) 186 (100), 77 (38), 63 (32), 263 (20), 187 (15), 327 (10, M). ^{1}H NMR ($CDCl_3$): δ 2.70 (2- or 3-Me, s), 2.73 (3- or 2-Me, s), 3.28 (NMe, s), 7.4–7.6 (5-H and Ph, m), 7.75 (7-H, dd), 7.96 (8-H, dd); $|J|$ 0.6 (5,8), 2.3 (5,7), 8.9 (7,8) Hz.

Acknowledgements. We are thankful to the Foundation for Promotion of Cancer Research, Tokyo, Japan, and the Swedish Council for Forestry and Agricultural Research for financial support. We thank Miss Ewa Raźnikiewicz, Mr. Jan-Olov Persson and Mr. Karl-Olof Schoeps for technical assistance. Mr. Rolf Andersson and Mr. Suresh Gohil are acknowledged for recording the spectra. We thank Professor Olof Theander for his kind interest.

References

1. Adolfsson, L. and Olsson, K. *Acta Chem. Scand. B 37* (1983) 157.
2. Grivas, S. and Olsson, K. *Acta Chem. Scand. B 39* (1985) 31.
3. Grivas, S. *Ibid.*, 213.
4. Miller, A. J. *Food Technol. 39* (1985) 75; Vuolo, L. and Schuessler, G. *Environ. Mutagen. 7* (1985) 577.
5. Sugimura, T. *Mutat. Res. 150* (1985) 33.
6. Negishi, C., Wakabayashi, K., Tsuda, M., Sato, S., Sugimura, T., Saito, H., Maeda, M. and Jägerstad, M. *Mutat. Res. 140* (1984) 55.
7. Jägerstad, M., Olsson, K., Grivas, S., Negishi, C., Wakabayashi, K., Tsuda, M., Sato, S. and Sugimura, T. *Mutat. Res. 126* (1984) 239; Grivas, S., Nyhammar, T., Olsson, K. and Jägerstad, M. *Mutat. Res. 151* (1985) 177; Taylor, R., Fulz, E. and Knize, M. *J. Environ. Sci. Health A 20* (1985) 135; Yoshida, D., Saito, Y. and Mizusaki, S. *Agric. Biol. Chem. 48* (1984) 241.
8. Jägerstad, M., Laser Reuterswärd, A., Öste, R., Dahlqvist, A., Grivas, S., Olsson, K. and Nyhammar, T. *Am. Chem. Soc. Symp. Ser. 215* (1983) 507; Jägerstad, M., Laser Reuterswärd, A., Olsson, R., Grivas, S., Nyhammar, T., Olsson, K. and Dahlqvist, A. *Food Chem. 12* (1983) 255.

9. Sugimura, T. and Sato, S. *Cancer Res. Suppl. 43* (1983) 2415s; Ames, B. N., McCann, J. and Yamasaki, E. *Mutat. Res. 31* (1975) 347.
10. Okamoto, T., Shudo, K., Hashimoto, Y., Kosuge, T., Sugimura, T. and Nishimura, S. *Chem. Pharm. Bull. 29* (1981) 590; Yamazoe, Y., Shimada, M., Kamataki, T. and Kato, R. *Cancer Res. 43* (1983) 5768.
11. Nagao, M., Fujita, Y., Wakabayashi, K. and Sugimura, T. *Biochem. Biophys. Res. Commun. 114* (1983) 626.
12. Watanabe, T., Yokoyama, S., Hayashi, K., Kasai, H., Nishimura, S. and Miyazawa, T. *FEBS Lett. 150* (1982) 434; Caderni, G., Kreamer, B. L. and Dolara, P. *Food Chem. Toxicol. 21* (1983) 641.
13. Ohgaki, H., Kusama, K., Matsukura, N., Morino, K., Hasegawa, H., Sato, S., Takayama, S. and Sugimura, T. *Carcinogenesis 5* (1984) 921; Takayama, S., Nakatsuru, Y., Masuda, M., Ohgaki, H., Sato, S. and Sugimura, T. *Gann 75* (1984) 467; Ohgaki, H., Hasegawa, H., Kato, T., Suenaga, M., Ubukata, M., Sato, S., Takayama, S. and Sugimura, T. *Proc. Jpn. Acad. B61* (1985) 137.
14. Felton, J. S., Knize, M. G., Wood, C., Wuebbles, B. J., Healy, S. K., Stuermer, D. H., Bjeldanes, L. F., Kimble, B. J. and Hatch, F. T. *Carcinogenesis 5* (1984) 95.
15. Le Bris, M.-T. *Bull. Soc. Chim. Fr.* (1976) 921.
16. Dewar, M. and Maitlis, P. *J. Chem. Soc.* (1957) 2518; Otomasu, H. and Nakajima, S. *Chem. Pharm. Bull. 6* (1958) 566; Nasielski-Hinkens, R., Benedek-Vamos, M. and Maetens, D. *J. Heterocycl. Chem. 17* (1980) 873.
17. Abdel-Hay, F. I. and Anwar, M. *Egypt. J. Chem. 25* (1982) 353; Nasielski-Hinkens, R. and Benedek-Vamos, M. *J. Chem. Soc. Perkin Trans. 1* (1975) 1229.
18. Quast, H. and Schmitt, E. *Chem. Ber. 101* (1968) 4012.
19. Myers, T. and Zeleznick, L. *J. Org. Chem. 28* (1963) 2087; Kasai, H., Yamaizumi, Z., Nishimura, S., Wakabayashi, K., Nagao, M., Sugimura, T., Spingarn, N. E., Weisburger, J. H., Yokoyama, S. and Miyazawa, T. *J. Chem. Soc. Perkin Trans. 1* (1981) 2290.
20. Vetesnik, P. *Coll. Czech. Chem. Commun. 33* (1968) 556.
21. Lee, C.-S., Hashimoto, Y., Shudo, K. and Okamoto, T. *Chem. Pharm. Bull. 30* (1982) 1857.
22. Wessely, F. and Swoboda, W. *Monatsh. Chem. 82* (1951) 621; Dannley, R. L., Lukin, M. and Shapiro, J. *J. Org. Chem. 20* (1955) 92.
23. Gilman, H. and Broadbent, H. S. *J. Am. Chem. Soc. 70* (1948) 2619.
24. Kasai, H., Shiomi, T., Sugimura, T. and Nishimura, S. *Chem. Lett.* (1981) 675.
25. Still, W. C., Kahn, M. and Mitra, A. *J. Org. Chem. 43* (1978) 2923.
26. Burton, D., Lambie, A., Lane, D., Newbold, G. and Percival, A. *J. Chem. Soc. (C)* (1968) 1268.
27. Czuba, W. and Poradowska, H. *J. Royal Netherl. Chem. Soc. 93* (1974) 162.
28. Grivas, S. and Jägerstad, M. *Mutat. Res. 137* (1984) 29; Nagao, M., Wakabayashi, K., Kasai, H., Nishimura, S. and Sugimura, T. *Carcinogenesis 2* (1981) 1147; Jägerstad, M. and Grivas, S. *Mutat. Res. 144* (1985) 131.

Received December 20, 1985.