M. Botta, F. De Angelis, R. Nicoletti

Institute of Organic Chemistry, University of Rome, 00185 Rome, Italy

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A new synthesis of 2-amino-3-methoxypyrazine, an intermediate in the synthesis of sulfalene, *via* 2-carbamido-3-hydroxy pyrazine and subsequent Hofmann rearrangement of 2-carbamido-3-methoxypyrazine, is described.

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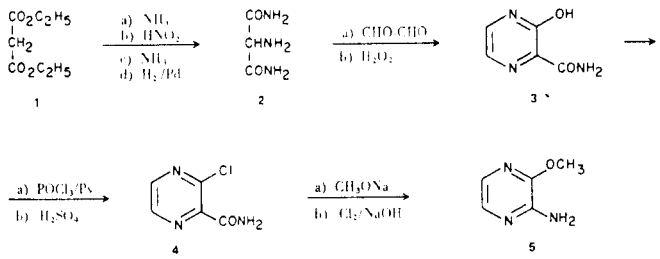
2-Sulfanilamido-3-methoxypyrazine (1) is a chemotherapeutic sulfanilamido derivative originally synthesized in the Farmitalia laboratories. It is currently clinically used under the name of sulfalene or kelfizine (2). The preparation of the key intermediates in the synthesis of this drug, 2,3-dichloropyrazine (3) and 2,3,5-trichloropyrazine (4), are covered by patents. Another possible intermediate, 2-amino-3-methoxypyrazine (**5**) was also obtained by the Farmitalia group through a complex route involving several steps (5).

We have now developed a synthetic method to obtain **5** in a few steps, with reactions suitable for large scale preparations (see Scheme 1). The starting material used was 2-carbamido-3-hydroxypyrazine (**3**), which can be obtained in good yield from glyoxal sodium bisulfite and aminomalondiamide (6). However, the availability of the latter, which can be obtained from diethylaminomalonate (7a-b) and ammonia in ethanolic solution (8) is limited by the large amount of catalyst required for the hydrogenation of isonitrosomalonate. Therefore, we developed a more convenient synthesis of aminomalondiamide (see Scheme 1).

Scheme 1



Diethylmalonate **1** was converted with ammonia in aqueous solution into malondiamide. Reaction of the crude amide with sodium nitrite in acetic acid-water solution yielded, after saturation with ammonia, an ammonium salt of isonitrosomalondiamide. Catalytic reduction in water gave very pure aminomalondiamide **2** in 48% overall yield.

Aminomalondiamide was condensed with glyoxal (commercial aqueous solution), previously converted into the bisulfite derivative by treatment *in loco* with sodium metabisulfite. As reported in the literature (6) for the reaction with the glyoxal-bisulfite adduct, 2-carbamido-3-hydroxypyrazine (**3**) was obtained in 78% yield. The hydroxy pyrazine was then treated with a phosphorus oxychloride-pyridine solution.

Trial experiments have always shown that 2-cyano-3-chloropyrazine was formed during the reaction. However, when the reaction mixture was treated with concentrated sulfuric acid after the removal of excess phosphorus oxychloride and pyridine, 2-carbamido-3-chloropyrazine (**4**) was obtained in 86% of yield (crude). This compound proved not to be stable when warmed in presence of water, being reconverted into the starting hydroxy pyrazine. An analytical sample was obtained by preparative thin layer chromatography and subsequent crystallization from ethyl acetate.

Crude **4** was converted into 2-carbamido-3-methoxypyrazine by treatment with sodium methoxide in methanol. After removal of the methanol, the crude mixture was treated with aqueous sodium hypochlorite. Chloroform extraction of the water solution yielded 2-amino-3-methoxy pyrazine (**5**) in 70% of yield. The final product proved to be pure based on thin layer chromatographic analysis, m.p. 84-85°, after crystallization from petroleum ether 60-80°.

Sulfalene prepared according to the method reported (1) from the crude pyrazine **5** obtained by us had m.p. 174-176° (crude: lit. m.p. 168-175°). After crystallization from ethanol it had m.p. 179-181° (lit. m.p. 176°).

EXPERIMENTAL

Melting points are uncorrected. The mass spectrum was performed by an AEI MS 12 mass spectrometer. Thin layer chromatography was run on glass plates coated with a 0.25 mm (2 mm for preparative) layer of silica gel 60 F^{254} (Merck). Spots were observed with uv light. The elemental analysis was kindly performed by ACRAF Research Laboratories, Rome.

Aminomalondiamide (**2**).

Diethylmalonate **1** (100 g.) was dropped into ammonium hydroxide (32%) aqueous solution (300 ml.) over a period of 2 hours at 10-15° under vigorous stirring. When about 50 g. of diethylmalonate were added, the mixture was saturated with gaseous ammonia. A crystalline solid (malondiamide) precipitated at the end of the reaction and after 2 hours of standing almost all the solvent was removed *in vacuo*. To the crude solid, acetic acid (180 ml.) and water (160 ml.) were added. A saturated

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solution of sodium nitrite (52 g.) in water (about 50 ml.) was dropped into the mixture under stirring at 0-5° over a time period of 30 minutes. The temperature was allowed to rise to 25° in 3 hours, and the mixture was left to stand overnight. Gaseous ammonia was bubbled into the solution wiht cooling (T ⩽ 35°) under stirring, upon which the colour turned to yellow-green and a solid precipitated. After 1 hour of standing at 10°, the solid was collected by filtration and suspended in 150 ml. of water. 10% Palladium on charcoal (400 mg.) was added and the mixture was hydrogenated at 45 psi and room temperature (3 hours). After filtration of the catalyst (hot water was added in order to dissolve the crystalline solid) most of the water was removed *in vacuo*. The residual solid was then collected, yield 34 g. (48%) of crude **2** m.p. 193-194° (lit. m.p. 187-188° (8)). One spot on tlc (eluent: *n*-propyl alcohol-2% concentrated ammonium hydroxide in water 4:1).

In one experiment, the conversion of isonitrosomalonate into the amide was tried according to the following procedure. Diethylmalonate **1** (10 g.) in acetic acid (11.5 ml.) and water (16 ml.) was treated under stirring with sodium nitrite (13 g.) at 5° (added over a time period of 30 minutes). The temperature was left to rise to 30°. After 3-4 hours of standing, 10 ml. of concentrated ammonium hydroxide were added to the mixture with cooling (T ⩽ 35°). The mixture was then saturated with gaseous ammonia and left overnight in a closed vessel, giving a yellow solid. The mixture was resaturated with ammonia and left for 5 hours. The solid which precipitated was collected and hydrogenated as described above, yield 3.6 g. (51%) of **2** (same purity as that obtained by the previous procedure).

2-Carbamido-3-hydroxypyrazine (**3**).

A mixture of glyoxal (55 ml., 30% water solution and sodium metabisulfite (65.5 g.) in water (190 ml.) was heated at 65° for 1 hour. A crystalline solid precipitated. Crude 2 (34 g.) was added and the mixture was heated at 80° over a period of 3 hours. Sodium acetate (163 g.) was then added and 74 ml. of hydrogen peroxide (30%) were dropped into the solution with stirring and cooling (T ⩽ 55°). After standing overnight, the solid which separated was collected and crystallized from water (about 800 ml.). The yield of **3** was 31 g. (78%) including the second crop recovered by concentration of the mother liquor, m.p. 268° dec. (lit. m.p. 268° (6)). One spot was observed on tlc (eluent: concentrated ammonium hydroxide in water solution 0.4%) at Rf 0.83.

2-Carbamido-3-chloropyrazine (**4**).

Compound **3** (31 g.) was added to a mixture of freshly distilled phosphorus oxychloride (58.5 ml.) and water-free pyridine (22.1 ml.) over a period of 1 hour with efficient stirring. The additions were cautious at the beginning and the temperature was kept below 40° (caution! the reaction should not be frozen). The mixture was then gently heated at 50° for two hours and one hour at 80° with stirring. The excess phosphorus oxychloride was removed *in vacuo* (T ⩽ 70°) and to the residual syrup, concentrated sulfuric acid (48 ml.) was slowly added. The temperature was then brought to 60° for two hours. The solution was slowly poured into a stirred mixture of crushed ice (265 g.) and ammonium carbonate (180 g.). The final solution was then neutralized with ammonia (concentrated solution or gas). After 3-4 hours of standing, the solid which precipitated was collected and washed wiht a small amount of water. Accurate drying of the product at moderate temperature (30-40°) under vacuum yielded 30 g. of **4** (86%). The crude product was examined by tlc showing only one spot (9) at Rf 0.18 (eluent: chloroform-ethyl acetate 1:1). An analytical sample of **4** was sublimed at 105-110° (0.4 mm Hg), purified by preparative layer chromatography (chloroform-ethyl acetate 1:1) and crystallized from ethyl acetate, m.p. 189-190°; ms: m/e (relative intensity) 159 (16), 157 (52), 116 (32), 114 (100), 80 (60), 52 (62), 44 50.

Anal. Calcd. for $C_5H_4ClN_3O$: C, 38.12; H, 2.56; N, 26.66. Found: C, 37.98; H, 2.49; N, 26.41.

2-Amino-3-methoxypyrazine (**5**).

Crude **4** (30 g.) was suspended in anhydrous methanol (210 ml.). The mixture was heated at 60° and a solution of sodium (5.7 g.) in mathanol (150 ml.) was added over a period of few minutes. Stirring and heating were continued for 1 hour (10). The solution was then neutralized with acetic acid and the methanol distilled off under reduced pressure. The residue was dissolved in water (150 ml.) and previously cooled sodium hypochlorite (350 ml.; the solution contained not less than 4% of chlorine and 18% of sodium hydroxide) was added under cooling (0-5°) in few minutes. The mixture was stirred at 0-5° for one hour, then the temperature was *rapidly* brought to 90° and maintained for an additional hour. The cooled solution was then extracted wiht chloroform (6 x 50 ml.). The organic layer was shaken with 20 ml. of sodium chloride saturated solution and dried over sodium sulfate. The solvent was removed by atmospheric pressure distillation. The yield was 16.5 g. (70%) of pure **5** (one spot on tlc at Rf 0.25: chloroform-ethyl acetate 1:1 as eluent) which crystallized on standing, m.p. about 80°. An analytical sample was obtained by crystallization from petroleum ether 60-80°, m.p. 84-85° (lit. m.p. 80-82° (5)).

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(9) A possible impurity wiht higher Rf (about 0.55) corresponds to 2-cyano-3-chloropyrazine. It is present when phosphorus oxychloride is not completely removed before adding sulfuric acid.

(10) The end of the reaction can be checked by tlc. 2-Carbamido-3-methoxypyrazine has Rf 0.09 (chloroform-ethyl acetate 1:1 as eluent).