in their sign and order of magnitude only; these parameters suggest again the importance of the solvent sulfur dioxide in the cleavage of the C–Cl bond.

Experimental Section

NMR Experiments. Equilibria and kinetics were measured with a FT Bruker WP-60 instrument equipped with a BNC-28 microcomputer and a variable-temperature unit. Faster kinetics were first recorded as FID's in different sections of the computer memory and Fourier transformed at the end. The samples were prepared by condensing a measured quantity of sulfur dioxide in a NMR tube containing a weighed amount of covalent chloride **3** or **4**. For high-temperature experiments the tubes were sealed.

Materials. Sulfur dioxide and 2,3-dimethyl-2-butene (tetramethylethylene) are commercial products. Methanesulfenyl chloride[16] and 2,2,5,5-tetramethyl-3-hexyne (di-*tert*-butylacetylene)[17] were prepared according to published procedures.

2,3-Dimethyl-3-(methylthio)-2-chlorobutane (3). To an ice-cooled and stirred dichloromethane solution of tetramethylethylene (in slight excess) is added methanesulfenyl chloride in the same solvent dropwise. After 5 min at 0 °C and 10 min at room temperature, the solvent and excess olefin are removed under vacuum; a yellow oil is obtained: 97% yield; bp 74–78 °C (20 mmHg). Because of product sensitivity to moisture, a bad elemental analysis was obtained; before use the alcohol formed is to be removed under vacuum: NMR ($CDCl_3$) [SO_2, –60 °C] δ 2.14 [2.05], SMe; 1.74 [1.73], CMe_2Cl; 1.46 [1.42], CMe_2S.

(*E*)-2,2,5,5-Tetramethyl-3-(methylthio)-4-chloro-3-hexene (4). With the same procedure, methanesulfenyl chloride is added to an equimolar amount of di-*tert*-butylacetylene. After 1 h the solution is washed with sodium carbonate in water and water to neutrality. The solution is dried and the solvent removed at low pressure; a yellow oil is obtained: 96% yield; bp 110–120 °C (15 mmHg); NMR ($CDCl_3$) [SO_2, –50 °C] δ 2.18 [2.25], SMe; 1.48 and 1.41 [1.45 and 1.37], *tert*-butyls.

Anal. Calcd for $C_{11}H_{21}ClS$: C, 59.85; H, 9.6. Found: C, 59.65; H, 9.5.

Registry No. **3**, 77483-47-7; **4**, 63720-34-3; **5**, 79899-49-3; **6**, 63720-33-2; tetramethylethylene, 563-79-1; methanesulfenyl chloride, 5813-48-9; di-*tert*-butylacetylene, 17530-24-4.

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(17) Hennion, G. F.; Banigan, T. F., Jr. *J. Am. Chem. Soc.* **1946**, *68*, 1202.

Studies in the Heterocyclic Series. 22. New Chemistry of Azaphenothiazine and Its Precursors

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Received April 28, 1981

In continuation of our studies on triazaphenothiazines,[2-5] we now report the synthesis of the parent 1,4,6-triaza compound **1a**. The route used involved the condensation of 2,3-dichloropyrazine (**2**) with 3-aminopyridine-2(1*H*)-thione (**3**, R = H).

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(2) C. O. Okafor, *J. Org. Chem.*, **38**, 4386 (1973).
(3) C. O. Okafor, M. L. Steenberg, and J. P. Buckley, *J. Heterocycl. Chem.*, **12**, 813 (1975).
(4) C. O. Okafor, *J. Heterocycl. Chem.*, **17**, 149 (1980).
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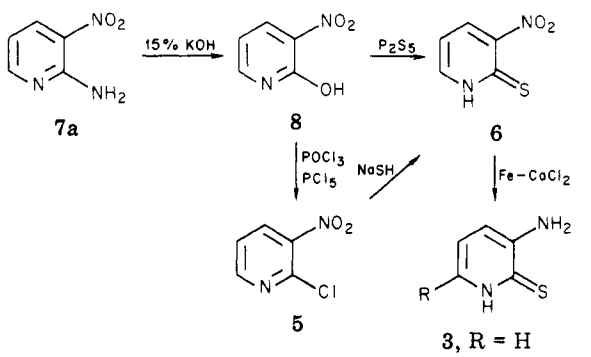
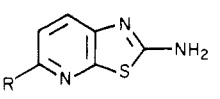
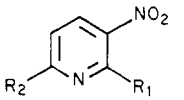
Scheme I



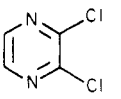
The key intermediate **3** (R = H) has been previously prepared[6,7] by the reaction of 3-amino-2-chloropyridine (**4**) with sodium hydrosulfide. Since the synthesis of **4** from nicotinamide has been found hazardous,[7] an alternative route to **3** (R = H) was developed by conversion of 2-chloro-3-nitropyridine (**5**) to the thione **6** and reduction with iron in the presence of calcium chlorides (Scheme I). The reagent is very convenient and permits facile isolation of the amine **3** in high yield. 3-Amino-6-methoxypyridine-2(1*H*)-thione (**3**, R = OCH_3) and the 6-chloro analogue (**3**, R = Cl) were obtained by the Fe–$CaCl_2$ reduction of the nitro compounds **7b** and **7c** followed by thiocyanation and alkaline hydrolysis of the intermediate thiazolo[5,4-*b*]pyridines (**9**).[8]



9, R = OCH_3; Cl

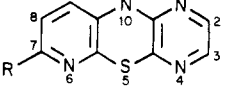


7a, R_1 = NH_2; R_2 = H
b, R_1 = H; R_2 = OCH_3
c, R_1 = H; R_2 = Cl

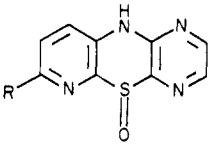


2

The reaction of an alkaline solution of the aminopyridinethiones with 2,3-dichloropyrazine (**2**) in propylene glycol or DMF gave greenish yellow solids whose composition and spectral properties were consistent for the 1,4,6-triazaphenothiazines **1** (R = H, OCH_3, Cl).



1a, R = H
b, R = OCH_3
c, R = Cl



10a, R = H
b, R = OCH_3
c, R = Cl

These 1,4,6-triazaphenothiazines were also converted to their 5-sulfoxides by the action of mixed concentrated nitric and sulfuric acids.

Experimental Section

General Methods. Melting points were determined with a Fisher-Johns apparatus and are uncorrected. UV and visible spectra were recorded on a Pye Unicam SP 8000 spectrophotometer using matched 1-cm quartz cells. The solvent was methanol, and the absorption maxima are always given in nanometers; the figures in parentheses are ϵ values. IR spectra were obtained on a Perkin-Elmer Model 137 spectrophotometer using potassium bromide disks unless otherwise stated. ^1H NMR

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(7) O. R. Rodig, R. N. Collier, and R. K. Schlatzer, *J. Org. Chem.*, **29**, 2652 (1964).
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0022-3263/82/1947-0592$01.25/0

spectra were determined on a Varian Associates T-60 instrument. Chemical shifts are reported on the δ scale relative to Me_4Si used as an internal standard. The letters br, s, d, t, q, sh, and m are used to indicate broad, singlet, doublet, triplet, quartet, shoulder, and multiplet, respectively. The mass spectra were obtained on an AEI MS-9 double-focusing mass spectrometer at 70 eV.

3-Nitro-2-pyridinol (8) from 2-Amino-3-nitropyridine. To 27.8 g (200 mmol) of 2-amino-3-nitropyridine in 200 mL of water was added 30 g of potassium hydroxide. The mixture was refluxed on a steam bath (temperature 92 °C) for 13 h. There was copious evolution of ammonia after 3 h, and complete dissolution of the 2-amino-3-nitropyridine was observed after 8 h.

At the end of the reflux period the dark yellowish red solution was cooled and then neutralized with concentrated hydrochloric acid to pH 2 with constant cooling. The dark precipitate was collected by vacuum filtration and crystallized twice from ethanol after treatment with activated charcoal to yield 3-nitro-2-pyridinol (8) as glistening yellow needles: 24.4 g (87% yield); mp 223–224 °C (lit.[9] mp 224 °C).

3-Nitropyridine-2(1*H*)-thione (6). This compound was prepared by an extensive modification of a procedure described in the literature.[10] 2-Chloro-3-nitropyridine (15.85 g, 100 mmol) was placed in a reaction flask containing 16.8 g of sodium hydrosulfide. Methanol (150 mL) was then added and the mixture refluxed for 10 h. It was then acidified with glacial acetic acid and cooled. After the mixture was filtered, the crude product was collected and recrystallized twice from ethanol after treatment with activated charcoal to yield 3-nitropyridine-2(1*H*)-thione (6) as yellow plates: 11.23 g (72% yield); mp 175–176 °C (lit.[10] mp 174–175 °C).

This compound was also prepared in 75% yield by the action of P_2S_5 to 3-nitro-2-pyridinol (8) as was described by Wise and Castle for the preparation of 5-aminopyridazine-6(1*H*)-thione.[11]

Fe–$CaCl_2$ Reduction of 3-Nitropyridine-2(1*H*)-thione (6). 3-Nitropyridine-2(1*H*)-thione (6; 31.2 g, 200 mmol) and 80 g of iron powder were placed in the reaction flask containing 500 mL of 75% ethanol. About 15 g of calcium chloride was then added and the entire mixture refluxed on a steam bath for 4.5 h.

At the end of the reflux period, the mixture was filtered hot to remove excess iron. The filtrate was again boiled and treated with activated charcoal followed by filtration. The filtrate was concentrated to near dryness. The crude residue was purified by crystallization from methanol (Norit A) to yield greenish yellow needles of 3-aminopyridine-2(1*H*)-thione (3, R = H): 21.42 g (85% yield); mp 131–132 °C lit.[7] mp 131–133 °C).

6-Substituted 3-Aminopyridine-2(1*H*)-thiones (3, R = OCH_3, Cl). These compounds were prepared as previously described[8] except that the reduction of the starting nitropyridines was accomplished by the Fe–$CaCl_2$ reagent as was described for compound 3 (R = H).

1,4,6-Triazaphenothiazine (1a). 3-Aminopyridine-2(1*H*)-thione (3, R = H) (6.30 g, 50 mmol) was placed in a 250-mL three-necked flask containing 30 mL of water and 6.00 g of sodium hydroxide. The mixture was warmed on a steam bath to dissolve the reactants. Propylene glycol (80 mL) was then added followed by the addition of freshly prepared 2,3-dichloropyrazine[12] (8.20 g, 55 mmol). The entire mixture was refluxed on a heating mantle for 7 h.

At the end of the reflux period, it was poured into a beaker containing 500 mL of water, stirred and cooled at −10 °C. After the mixture was filtered, crystallized from ethanol, and treated with activated charcoal, 1,4,6-triazaphenothiazine[13] (6.77 g, 67% yield) was obtained as greenish yellow powder: mp 213–214 °C; IR ν_{max} 3200 (10-NH), 813 (2,3-disubstituted pyrazine) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 7.77 (m, area 3, 7-H, 8-H, 9-H), 8.40 (s, area 2, 2-H, 3-H), 9.50 (br s, 10-NH); mass spectrum, *m/e* (relative intensity) 201 (6), 202 (M^+, 100), 203 (10).

Anal. Calcd for $C_9H_6N_4S$: C, 53.47; H, 2.97; N, 27.72; S, 15.84. Found: C, 53.53; H, 2.76; N, 27.70; S, 15.95.

7-Methoxy-1,4,6-triazaphenothiazine (1b). 3-Amino-6-methoxypyridine-2(1*H*)-thione (3, R = OMe; 15.6 g, 100 mmol) and 10 g of sodium hydroxide were placed in the reaction flask to which was also added 40 mL of water. The mixture was warmed to dissolve the reactants. 2,3-Dichloropyrazine (17.88 g, 120 mmol) and 80 mL of *N,N*-dimethylformamide were then added. The entire mixture was refluxed on the heating mantle for 3.5 h.

At the end of the reflux period, the mixture was poured into a beaker containing 1 L of water, chilled overnight, and filtered. The residue was crystallized twice from aqueous DMAC after treatment with activated charcoal. 7-Methoxy-1,4,6-triazaphenothiazine was obtained as glistening greenish yellow microneedles: 20.65 g (89% yield); mp 211–212 °C; IR ν_{max} 3230 (10–NH), 820 (2,3-disubstituted pyrazine) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.67 (s, 7-OCH_3), 6.37 (d, J = 8.8 Hz, 8-H), 7.00 (d, J = 8.8 Hz, 9-H), 7.53 (s, 2-H, 3-H), 9.17 (br s, 10-NH); mass spectrum *m/e* (relative intensity) 189 (79), 217 (29), 231 (11), 232 (M^+, 100), 233 (28).

Anal. Calcd for $C_{10}H_8N_4OS$: C, 51.72; H, 3.45; N, 24.14; S, 13.79. Found: C, 51.59, H, 3.48, N, 24.06; S, 13.68.

7-Chloro-1,4,6-triazaphenothiazine (1c). This compound was prepared from 3-amino-6-chloropyridine-2(1*H*)-thione (3, R = Cl; 12.04 g, 75 mmol), 8.00 g of sodium hydroxide, and 11.8 g (75 mmol) of 2,3-dichloropyrazine in 80 mL of DMF as described for 7-methoxy-1,4,6-triazaphenothiazine (1b).

7-Chloro-1,4,6-triazaphenothiazine was obtained as bright yellow powder: 14.37 g, (81% yield); mp 185–186 °C; IR ν_{max} 3433 (10-NH), 815 (2,3-disubstituted pyrazine) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 5.50 (br s, 8-H, 9-H), 7.27 (s, 2-H, 3-H), 8.35 (s, 10-NH); mass spectrum *m/e* (relative intensity) 201 (12), 236 (M^+, 100), 237 (22), 238 (47).

Anal. Calcd for $C_9H_5N_4ClS$: C, 45.67; H, 2.11; N, 23.68; Cl, 15.01; S, 13.53. Found: C, 45.83; H, 2.00; N, 23.69; Cl, 15.20; S, 13.34.

1,4,6-Triazaphenothiazine 5-Oxide (10a). Concentrated sulfuric acid (*d* 1.84, 25 mL) was precooled to near 0 °C and added to 2.02 g (10 mmol) of 1,4,6-triazaphenothiazine in a 100-mL flask. Concentrated nitric acid (*d* 1.42, 25 mL), also precooled to near 0 °C, was added gradually with cooling and stirring during a period of 30 min. After all the nitric acid had been added, the mixture was stirred at 10 °C for about 1 h and at room temperature for 10 h. It was allowed to stand overnight at room temperature. The cool mixture was later poured into crushed ice and neutralized with concentrated ammonia to pH 8. The impure product was collected by filtration and crystallized from aqueous ethanol to give of 1,4,6-triazaphenothiazine 5-oxide (10a) as a yellow powder: 1.25 g (62% yield) mp >202 °C dec; IR (KBr disk) ν_{max} 1053 (s, S=O) cm^{-1}.

Anal. Calcd for $C_9H_6N_4OS$: C, 49.53; H, 2.76; N, 25.68; S, 14.69. Found: C, 49.61; H, 2.69; N, 25.50; S, 14.66.

7-Methoxy-1,4,6-triazaphenothiazine 5-Oxide (10b). This compound was prepared in 76% yield as reported for 1,4,6-triazaphenothiazine 5-oxide: mp >195 °C dec; IR (KBr disk) ν_{max} 1044 (s, S=O) cm^{-1}.

Anal. Calcd for $C_{10}H_8N_4O_2S$: C, 48.39; H, 3.23; N, 22.58; S, 12.90. Found: C, 48.30; H, 3.35; N, 22.42; S, 13.03.

7-Chloro-1,4,6-triazaphenothiazine 5-Oxide (10c). 7-Methoxy-1,4,6-triazaphenothiazine 5-oxide was prepared in 69% yield as reported for 1,4,6-triazaphenothiazine-5-oxide (10a) except that crystallization was from aqueous ethanol; m.p. 154–156 °C dec; IR spectrum (KBr disk) ν_{max} 1040 (s, S=O) cm^{-1}.

Anal. Calcd for $C_9H_5N_4ClOS$: C, 42.77; H, 1.98; N, 22.18; Cl, 14.06; S, 12.67. Found: C, 42.86; H, 1.99; N, 22.20; Cl, 13.94.

Acknowledgment. We express our appreciation to the Senate Research Grants Committee of the University of Nigeria for its support of this work through Research Grant No. 00134/76. We also thank Professor C. Galeffi of Istituto Superiore di Sanita, Rome, Italy, for part of the

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(11) D. S. Wise, Jr., and R. N. Castle, *J. Heterocycl. Chem.*, **11**, 1001 (1974).

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(13) This compound was numbered as recommended by L. T. Capell and D. F. Walker, Jr., in "Ring Index, Supplement I", American Chemical Society, Washington, DC, 1963, p 112. The nomenclature is consistent with what is used in the current literature of phenothiazine chemistry as it brings out the structural relationship with the parent phenothiazine ring system. 1,4,6-Triazaphenothiazine can also be named pyrazino-[2,3-*b*][1,4]pyrido[3',2'-*e*]thiazine.

microanalysis and mass spectra. Grateful acknowledgement is also extended to Mr. A. Imo of the Department of Pure and Applied Chemistry, University of Strathelyde, Glasgow, Scottland, for parts of the microanalysis and mass and ultraviolet spectra. The technical assistance of Messrs. O. O. Ibe, N. Igwe, and F. U. Ekezie of these laboratories is highly appreciated.

Registry No. **1a**, 80127-31-7; **1b**, 80127-32-8; **1c**, 80127-33-9; **2**, 4858-85-9; **3** (R = H), 38240-21-0; **3** (R = OCH_3), 42362-14-1; **3** (R = Cl), 27467-92-1; **5**, 5470-18-8; **6**, 38240-29-8; **7a**, 4214-75-9; **8**, 6332-56-5; **10a**, 80127-34-0; **10b**, 80127-35-1; **10c**, 80127-36-2.

Studies Aimed at the Synthesis of Morphine. 3.[1] Synthesis of (±)-Salutaridine via Phenolic Oxidative Coupling of (±)-Reticuline

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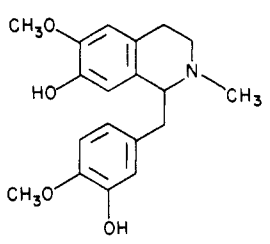
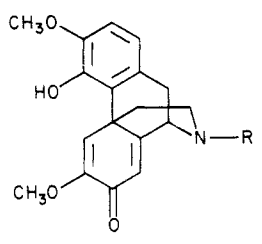
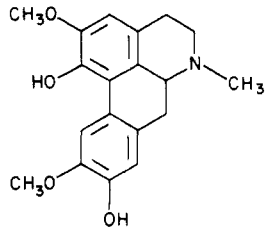
Robinson's seminal suggestions on the biogenesis of morphine[2] have been further refined by Barton[3] and have been supported by in vivo experiments involving the oxidation of reticuline (**1**) to salutaridine (**2a**) and the further transformation of this intermediate into morphine.[4,5]



1



2a, R = CH_3
b, R = CHO
c, R = H



3

The literature is replete with attempts to convert reticuline, into salutaridine in the laboratory, a transformation which involves para-ortho′ phenolic oxidative coupling (*p*–*o*′). Depending upon experimental conditions, however, only isoboldine (*o*–*p*′ coupling),[6] isosalutaridine (*p*–*p*′ coupling),[6] and corytuberine (*o*–*o*′ coupling),[7] were obtained. The first and so far sole successful transformation of this type was carried out by Barton and co-workers,[8] who oxidized tritium-labeled (±)-reticuline to (±)-salutaridine using potassium ferricyanide. The product was detected by an isotope-dilution technique and was present in 0.03% yield.

Schwartz and Mami[9] have found that appreciably improved yields (16–35%, corrected for recovered starting material[10]) of the desired *p*–*o*′ products could be accomplished starting with *N*-acylnorreticulines and using thallium tris(trifluoroacetate) as the oxidizing agent to produce *N*-acylnorsalutaridine derivatives.

In previously reported experiments we have obtained *N*-acyl- or 6′-halogeno-*N*-acylnorsalutaridines from the corresponding norreticuline derivatives in 14–58% yield, again correcting for recovered starting materials.[1]

We now describe the first in vitro replication of the in vivo process, namely, the conversion of (±)-reticuline (**1**) into (±)-salutaridine (**2a**) in preparative quantities. Additionally, this is the first report of the preparation of crystalline (±)-salutaridine.[11]

(±)-Reticuline (**1**),[12] in absolute dichloromethane (10^{-3} M) was treated with 0.5 equiv of lead tetraacetate in the presence of 3 molar equiv of trichloroacetic acid at −78 °C (4 h). Extraction of the crude product mixture in chloroform with 0.5–5% aqueous sodium hydroxide resulted in a facile separation of the crude monophenolic salutaridine and the diphenolic byproducts and starting material. TLC purification of the organic layer supplied (±)-salutaridine (**2a**) which was crystallized from EtOAc in 2.7% corrected yield. From the aqueous layer were obtained (±)-isoboldine (**3**, 14% corrected) and unreacted (±)-reticuline (**1**, 48%). Up to now neither (±)-isosalutaridine nor any well-defined other products could be isolated.[13]

The spectral data for the isolated (±)-salutaridine compare well with those cited in the literature.[4c,11,14] In ad-

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