N^1-Substitution in 2-Methyl-4(5)nitroimidazole. III. (1) New Syntheses of 1-(2′-(Ethylsulfonyl)ethyl)-2-methyl-5-nitroimidazole

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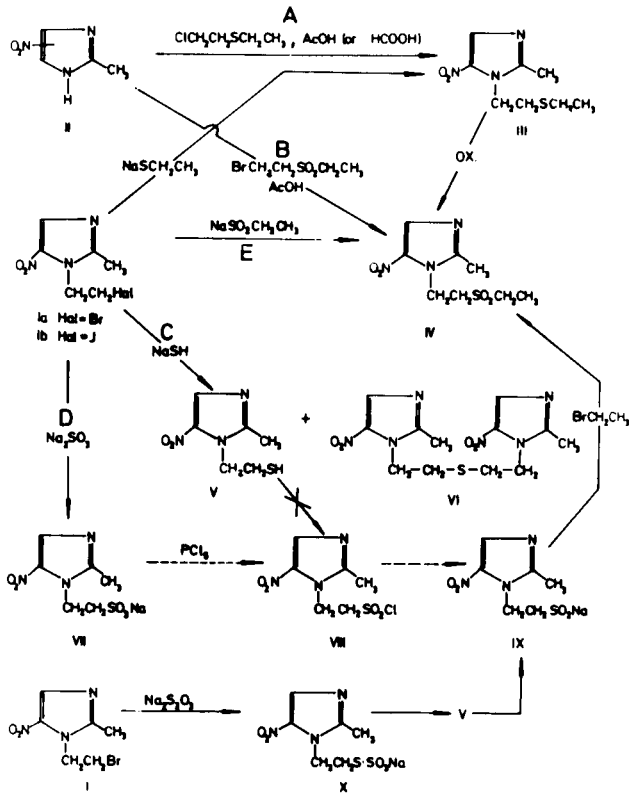
Some new syntheses of 1-[2′-(ethylsulfonyl)ethyl]-2-methyl-5-nitroimidazole (IV), a new antitrichomonal agent are described. The most successful method proved to be alkylation of sodium ethanesulfinate (XXI) with 1-(2′-haloethyl)-2-methyl-5-nitroimidazoles (Ia,b) in dimethylformamide.

In this paper synthetic investigations on the preparation of 1-[2′(-ethylsulfonylethyl]-2-methyl-5-nitroimidazole (IV-Scheme I) are described. This compound was recently introduced into chemotherapy as a highly potent antitrichomonal agent (2-5). Earlier preparations of this compound made use of oxidation of 2′-ethylthioethyl-2-methyl-5-nitroimidazole (III) to IV, or condensation of 2-methyl-4(5)nitroimidazole (II) with ethylsulfonylethyltosylate (6-8). Both methods afforded IV in low to moderate yields, 35% (6) and 17.6% (7), respectively.

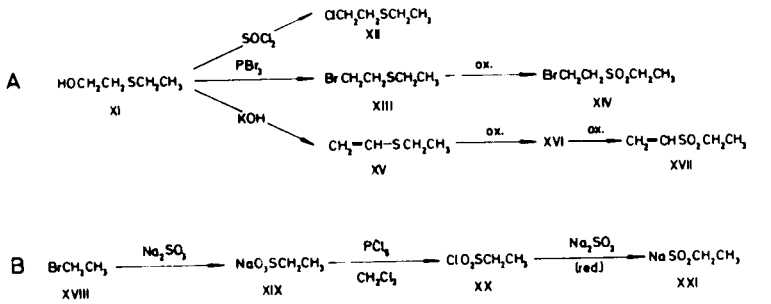
SCHEME I



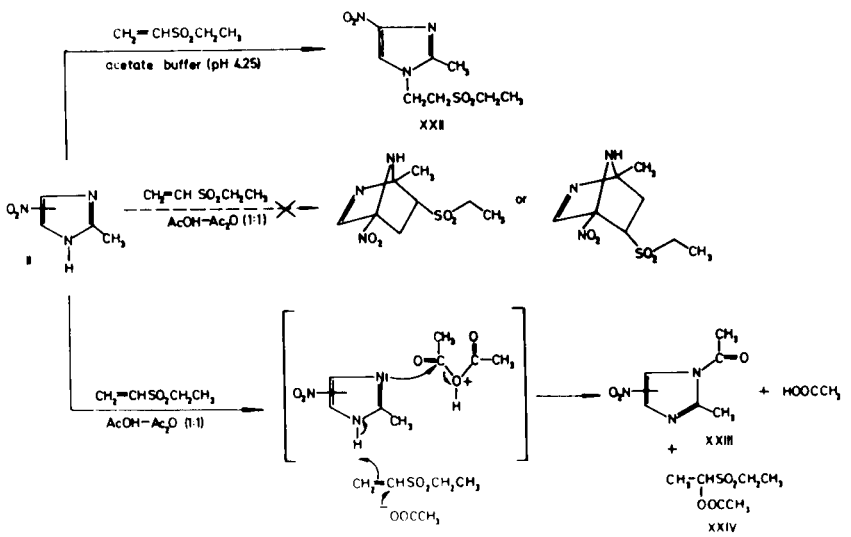
Continuing our earlier investigations an N^1-substitution in 2-methyl-4(5)nitroimidazoles (1,9,10), and particularly on 1-(4(5)nitro-2-methyl)imidazolyl ethers (9,11) we have prepared some thioethers, first described by Miller *et al.*, (7) along with the corresponding sulfones. We now describe some trials in the preparation of IV based on our earlier experience. Acid-catalysed condensation of II with ethyl 2-chloroethyl sulfide was primarily attempted (Scheme IA), because lower molecular weight carboxylic acids are very useful reaction media (1,9) for N^1-substitution of 4(5)nitroimidazoles in the course of these trials only the 5-nitro isomers which are very interesting compounds from a pharmacological point of view (10) were obtained. The reaction proceeded as expected, *i.e.* affording the 5-nitro isomer III in a moderate yield of 35%. Using the earlier described oxidation with hydrogen peroxide-acetic acid (6), III was converted into IV in limited yields. At this stage a violent explosion was experienced in work on batches containing *ca.* 5 g. of nitroimidazole. Probably the nitro compound is decomposed oxydatively in the presence of hydrogen peroxide or peracetic acid. This procedure, therefore, seems to be inappropriate for larger-scale preparations of IV. We consequently oxidized ethyl 2-bromoethyl sulfide (XIII) to the corresponding sulfone XIV before condensation with II. In acetic acid, condensation led to IV in low yield (Scheme IB).

In the second approach, compound Ia (9) was used as starting material, and two reaction sequences were carried out, *i.e.* Ia → V → VIII → IX → IV, and Ia → VII → VIII → IX → IV (Scheme IC and ID). Compound V was obtained from Ia in *ca.* 50% yield, along with some sulfide VI, the

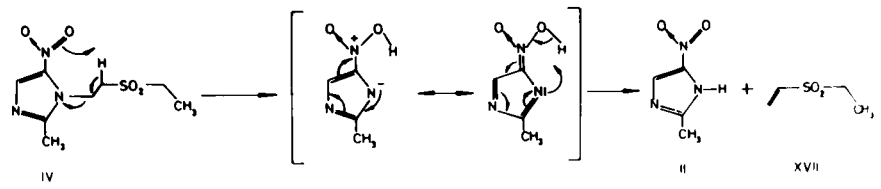
SCHEME II



SCHEME III



SCHEME IV



structure of which was confirmed by nmr and ir spectra, and unambiguously distinguished by elemental analysis from the disulfide compound which could also be formed from V. Another, indirect method of preparation gave better yields of V. Compound Ia was quantitatively converted into X (Bunte's salt (12)), and X with iodine gave the hydroiodide Va in 80% yield.

Oxidation of V to VIII using various agents, sodium hypochlorite, chlorine, *etc.*, was entirely unsuccessful, resulting in decomposition of the nitroimidazole moiety. Direct oxidation of V to IX in basic aqueous hydrogen peroxide solution gave very low yields of the desired product, which was not isolated because of its hygroscopic properties, but identified by its nmr spectrum, and unambiguously confirmed by further conversion into IV. The other reaction path (IID) proved also to be rather troublesome because of the difficulties in the first step. Compound VII proved to be a very hygroscopic material, which was identified as the barium salt. Its conversion to VIII without purification gave only traces of the desired product. Therefore we turned to the "reverse" procedure, *i.e.* preparation of sodium ethanesulfinate (Scheme IIB) and condensation with I in a suitable medium (Scheme IIE). This way proved to be most suitable one for the preparation of IV. Using

dry dimethylformamide as the solvent, IV was obtained in 50-60% yield after a simple isolation procedure. A number of other solvents were carefully tested for this condensation, their use resulted, however, in low yields and partial decomposition of the product. It appeared, as shown by tlc, that the reaction in boiling acetonitrile or dioxane did not take place at all, while slow conversion and low yields of IV were obtained when nitromethane or 1-propanol were used. A faster reaction was observed in boiling ethanol-water (1:1), or dimethylsulphoxide at 120°, but competitive decomposition of IV and formation of a new spot of II was observed, thus indicating cleavage of the N^1-C bond in compound IV. This reaction can be explained in the same manner as the decomposition of some aryl-β-carboxyethylsulfones (13), *i.e.* through the intramolecularly-induced elimination of vinylethylsulfone XVII (Scheme IV). This was proved by independent experiments, where 5- and 4-nitro isomers (IV and XXII) were heated under identical conditions in ethanol-water (1:1). Decomposition and formation of II was only observed in IV. Thus dimethylformamide remains the solvent of choice for the preparation of IV. The same was stated previously for the alkylation of some arylsulphinates (13). Surprisingly, very slow conversion in acetone was observed although this solvent was found in an extensive study (14) to be optimal for alkylation of some arylsulfinates.

The catalytic activity of sodium iodide on the alkylation of ethanesulfinate was investigated because similar activity had been observed earlier (14). The same yields of IV were obtained with or without the presence of catalytic amounts of sodium iodide in DMF. It seems that halogen exchange (Ia → Ib) is not faster than alkylation of ethanesulfinate. Working with Ib, however, lower reaction temperature and higher purity of the product have been achieved. Recently Kornblum observed (15) that α-iodonitroalkanes better alkylate arylsulfinates than the corresponding α-bromo compounds. It seems to us, based on the different reactivity observed for Ia and Ib, that this finding is valid for unactivated primary haloalkanes as well.

The preparation of sodium ethanesulfinate, though simple in view of the reactants used, presented some difficulties because of the limited and partly inaccurate data on the intermediates dispersed in the literature (16,17). Therefore we describe in some detail the procedures used.

A third way for the preparation of IV was investigated as well (Scheme III). This was based on a report (18) describing the addition of pyrazole to the double bond of α-acetomidoacrylic acid in acetic acid or acetate buffer (*p*H 4.25), affording α-acetamido-β-(*N*-pyrazolyl)propionic acid, and on the known addition reactions of imidazoles to alkenysilanes (19). Vinlethylsulfone (XVII) was prepared from ethyl (2-hydroxyethyl) sulfide (XI) which was dehydrated to XV (potassium hydroxide, 56% yield after distillation, b.p. 91-93°) and XV was oxidized to XVII. Addition of XVII to II (Scheme III) in acetate buffer led only to the 4-nitroisomer XXII. Its structure was confirmed by nmr spectroscopy according to our previous investigations (20). Compound XXII can be separated from IV by gas chromatography and identified by its mass spectrum as well (21). Addition did not take place at all when attempted in 90% acetic or formic acid, or in glacial acetic acid. In a mixture of glacial acetic acid-acetic anhydride (1:1) only one compound was formed, as shown by tlc, but its Rf differs substantially (Rf 0.85-0.90 in ether-acetone (3:1) as eluent) from that of IV (Rf 0.45). All our attempts to isolate this compound by careful evaporation of the solvent *in vacuo* proceeded by crystallization to inert solvents, or by chromatography on silica gel quantitatively produced starting compound II. This indicates the high instability of the product formed, so that our former assumption that a product of Diels-Alder $4\pi + 2\pi$ addition (Scheme III) was formed, has been ruled out solely on the basis of the observed instability of this compound. Vinylalkysulphone as dienophile in the Diels-Alder reaction is, however, described in the literature (22). From the nmr data we concluded that N^1-acetyl-2-methyl-5-nitroimidazole (XXIII), a highly unstable imide-like compound, is formed. Similar acylation of an sp^2-hybridized nitrogen atom with protonated acetic anhydride has recently been described (23). In our reaction vinylsulfone probably serves as a proton acceptor because no reaction was observed when this compound was absent from the reaction mixture (Scheme III). Thus the 5-nitroisomer IV could not be prepared by addition of vinylethylsulfone to II, and in view of the aforementioned results the most convenient procedure for its preparation proved to be the condensation of compounds Ia,b with sodium ethanesulfinate in dimethylformamide.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Infrared spectra were taken on a Perkin-Elmer Model 257 on Unicam SP 200 Spectrophotometer in potassium bromide pellets unless otherwise stated. Nmr spectra were recorded on a Varian T-60 Spectrometer using TMS as the internal standard, except when deuterium oxide was a solvent in which case the sodium salt of DSS was used. Tlc was carried out on Merck F_{254} silical gel plates. Spots were detected with a uv-lamp (λ-254 nm) or in iodine vapours. For column chromatography, silica gel 0.05-0.2 mm (Merck) was used.

1-(2′-Ethylthioethyl)-2-methyl-5-nitroimidazole (III).

Method A.

Compound XII was prepared by adding dropwise ethyl (2-hydroxyethyl) sulfide (XI) (21.5 ml., 0.202 mole) during 20 minutes into the stirred and cooled solution of thionyl chloride (28.0 ml., 46.5 g., 0.39 mole) in chloroform (180 ml.). After stirring at 0-3° for 2 hours and overnight at room temperature, the solvent was distilled off, 20.7 g. (69.5%) of ethyl (2-chloroethyl) sulfide (XII) with b.p. 68-70°/45 mm was obtained (lit. (24) b.p. 55-56°/

30 mm). To XII (11.6 ml., 12.38 g., 84 mmoles) in glacial acetic acid (13 ml.), compound II (1.78 g., 14 mmoles) was added. The reaction mixture was stirred at 90° for 4.5 hours. Thereafter solvent and excess XII were distilled off. The residue was diluted with water and made alkaline with 15% sodium hydroxide (*p*H 7.5-8). After extraction with ether (4 x 100 ml.) the combined ethereal extracts were dried (sodium sulfate), evaporated *in vacuo* and the crude material purified by column chromatography (105 x 1.7 cm, 100 g. of silica gel) with acetone as the eluent. A pale-yellow oil was obtained, 1.133 g. (35%) of 1-(2′-ethylthioethyl)-2-methyl-5-nitroimidazole (III); ir (neat): 2970 (s), 2930 (s), 1645 (m), 1525 (s), 1425 (s), 1360 (s) and 685 (m) cm^{-1}; nmr (carbon tetrachloride): δ 1.20 (t, 3H), 2.50 (s, 3H), 2.60 (q, 2H), 2.82 (t, 2H), 4.45 (t, 2H) and 7.80 ppm (s, 1H). Picrate (recrystallized from 96% ehtanol m.p. 124-126°; nmr (acetone-d_6): δ 1.25 (s, 3H), 2.65 (q, 2H), 2.90 (s, 3H), 3.12 (t, 2H), 4.82 (t, 2H), 6.80 (s, 2H), 8.40 (s, 1H) and 9.90 ppm (s, 1H).

Anal. Calcd. for $C_{14}H_{16}N_6O_9S$ (444.399): C, 37.84; H, 3.63; N, 18.91. Found: C, 38.04; H, 3.90; N, 18.72.

A complex with mercuric chloride was prepared and recrystallized from 96% ethanol, white needles, m.p. 109.5-112°; ir (potassium bromide): 3138 (m), 2980 (m), 2928 (m), 1540 (s), 1490 (s), 1476 (s), 1428 (s), 1368 (s), 1264 (s), 1190 (s) and 1146 (s) cm^{-1}.

Method B.

Compound Ia (11.7 g., 50 mmoles) was dissolved in absolute ethanol (180 ml.) and a previously prepared ethanolic solution of sodium thioethylate [from sodium (1.157 g., 50.3 mmoles) in absolute ethanol (32.5 ml.) and 3.8 ml. (3.1 g., 50 mmoles) of ethanthiol] was added. The solution was refluxed for 15 minutes and stirred for 2-3 hours at room temperature. The reaction mixture was concentrated, some ether added, and the precipitated sodium bromide removed by filtration. The filtrate was evaporated *in vacuo* to dryness and the dark oily residue purified by column chromatography (150 x 2.8 cm, 320 g. of silica gel) with ethyl acetate as the eluent. Fractions containing pure III were combined, evaporated *in vacuo* and dissolved in ether. The ethereal solution was decolorized by passing through a column of activated charcoal (0.5 x 2.6 cm) and silica gel (3.0 x 2.6 cm). After removing the solvent *in vacuo*, 10.2 g. (95%) of III was isolated. The nmr spectrum was identical with that of the sample prepared by the first method.

1-[2′-(Ethylsulfonyl)ethyl]-2-methyl-5-nitroimidazole (IV).

Method A.

Compound Ib (2.25 g., 8 mmoles) was dissolved in dry DMF (40 ml.) and sodium ethanesulfinate (XXI) (2.79 g., 24 mmoles) was added portionwise during 2.5 hours. The reaction mixture was heated at 60° with stirring for 3 hours and DMF was distilled off under reduced pressure (b.p. 40-41°/11 mm Hg). The residue was slurried in water (50 ml.) and extracted with ethyl acetate (200 ml.). The combined extracts were dried (sodium sulfate) and evaporated *in vacuo*. The residual oil crystallized on standing. The crystals were suspended in benzene and collected by filtration; 1,174 g. (59.2%) of 1-[2′-(ethylsulfonyl)ethyl]-2-methyl-5-nitroimidazole (IV) were obtained, m.p. 122-126°, one spot on tlc. Once recrystallized from 96% ethanol the product melted at 124.5-127° (lit. (7) m.p. 127-128°). Satisfactory elemental analysis, ir and nmr spectra were obtained. Picrate, m.p. 162-163° (recrystallized from 97% ethanol); nmr (perdeuterionitromethane): δ 1.37 (t, 3H), 2.75 (s, 3H), 3.18 (q, 2H), 4.95 (t, 2H), 8.15 (s, 1H) and 9.05 ppm (s, 1H).

Anal. Calcd. for $C_{11}H_{16}N_6O_{11}S$ (476.377): C, 35.30; H, 3.39; N, 17.65. Found: C, 35.42; H, 3.33; N, 17.47.

Method B.

Compound III (4.3 g., 20 mmoles) was dissolved in glacial acetic acid (20 ml.) and 30% hydrogen peroxide (6.15 ml., 60 mmoles) was added. After stirring at 60-80° for 5 hours or at room temperature for three days, the reaction mixture was evaporated to dryness. The residue was crystallized from benzene; 1.6355 g. (33%) of IV, m.p. 118-124° was obtained as orange needles. Further recrystallization from 96% ethanol gave the pure sample, m.p. 125-127°.

Method C.

The intermediary ethyl (2-bromoethyl) sulfone (XIV) was prepared as follows. Compound XI (20 ml., 19.96 g., 0.188 mole) was added dropwise with stirring into a suspension of phosphorus tribromide (17.8 ml., 50.8 g., 0.187 mole) in dichloromethane (160 ml.) at -10°. After stirring in an ice-bath for 2 hours and overnight at room temperature, the reaction mixture was poured into crushed ice-water and the *p*H adjusted to 4.5. After separating the aqueous layer it was extracted twice with dichloromethane (300 ml.). The combined extracts were dried (calcium chloride and sodium sulfate) and evaporated *in vacuo*. The residue was distilled; 28.855 g. (90.7%) of ethyl (2-bromoethyl) sulfide (XIII) was obtained, b.p. 36-38° at 1 mm (lit. (25) b.p. 57-58° at 6 mm). Compound XI (15 g., 88.8 mmoles) was oxidized in glacial acetic acid (90 ml.) with 30% hydrogen peroxide (27.1 ml., 266 mmoles). After stirring at 60-70° for 24 hours, the mixture was diluted with 500 g. of crushed ice and water and extracted with dichloromethane (600 ml.). The organic layer was washed (3x with saturated aqueous sodium bicarbonate, 1x with 5% ferrous sulfate and water) and dried (sodium sulfate). After evaporating, the residual oil was redistilled and 7.892 g. (44.3%) of ethyl (2-bromoethyl) sulfone (XIV) were obtained, b.p. 107-110° at 2 mm (lit. (25) b.p. 126-128° at 3.5 mm).

Compound II (492 mg., 3.87 mmoles) was added to the solution of XIV (2.34 g., 11.6 mmoles) in glacial acetic acid (4.9 ml.). The reaction mixture was heated to 80° for 24 hours. The solvent and excess of XIV were distilled off under reduced pressure. Hot water (20 ml.) was added to the residue and filtration with activated charcoal was performed. Some unreacted II precipitated upon cooling and was collected by filtration (281 mg., 57%). The filtrate was made alkaline to *p*H 9 and extracted with ethyl acetate (100 ml.). The combined extracts were dried (sodium sulfate) and evaporated to dryness. The crude product was crystallized from 96% ethanol, 93 mg. (9.7%) of IV, m.p. 118-122° was obtained.

Method D.

Compound V (936 mg., 5 mmoles) was dissolved in acetone (30 ml.), 30% hydrogen peroxide (2.55 ml., 25 mmoles) and 2*N* sodium hydroxide (5.00 ml., 10 mmoles) was added gradually, in small portions during 10 hours. After refluxing for 11 hours the reaction mixture was evaporated to dryness. The product, (1.5 g.) sodium 2-(2′-methyl-5′-nitro)imidazolylethanesulfinate (IX), was a very hygroscopic brown mass and any purification was unsuccessful; nmr (deuterium oxide): δ 2.55 (s, 3H), 3.35 (t, 2H), 4.73 (t, 2H), and 8.03 ppm (s, 1H).

The crude IX (1.5 g.) was stirred in dry DMF (25 ml.) with bromoethane (1.5 ml., 2.18 g., 20 mmoles) for 4.5 hours at 80-90°. Thereafter, DMF was distilled off (45-47° at 15 mm). The residue was slurried in water (25 ml.) and extracted with ether (4 x 30 ml.). The combined extracts were dried (sodium sulfate) and evaporated. The residual oil (0.3 g.) was separated by column chromatography: 68 x 0.8 cm., 12 g. of silica gel, eluent ether-acetone 3:1, to give

25.0 mg. (2%) of product IV which was recrystallized from 96% ethanol, m.p. 120-124°.

1-(2′-Thioethyl)-2-methyl-5-nitroimidazole (V).

Method A.

Compound Ia (2.34 g., 10.0 mmoles) and sodium hydrogen sulfide monohydrate (0.78 g., 10.5 mmoles) were dissolved in a mixture of ethanol (40 ml.) and water (4 ml.). After 20 hours stirring at room temperature, the precipitated sodium bromide was collected by filtration and the filtrate evaporated to dryness. The organic substance was separated from the remaining sodium bromide by dissolving in ethanol. The ethanol was removed *in vacuo* and a dark oily residue (2.00 g.) was separated by column chromatography (105 x 1.7 cm, 100 g. of silica gel). Elution with ethyl acetate gave 450 mg. (19.2%) of starting material Ia, m.p. 75-78°, and 879 mg. (47%) of 1-(2′-thioethyl)-2-methyl-5-nitroimidazole (V), m.p. 118-121°. Recrystallization from 96% ethanol yielded the pure sample with m.p. 122-124°; ir (potassium bromide): 1610 (m), 1535 (s), 1495 (s), 1370 (s), 1312 (s), 1190 (s), 830 (s) and 725 (s) cm^{-1}; nmr (acetone-d_6): δ 1.48 (s, 1H), 1.95 (s, 3H), 2.70 (t, 2H), 4.15 (t, 2H) and 7.35 ppm (s, 1H).

Anal. Calcd. for $C_6H_9N_3O_2S$ (187.218): C, 38.50, H, 4.85. Found: C, 38.72; H, 4.71.

Picrate (recrystallized from 96% ethanol) m.p. 196-198°.

Anal. Calcd. for $C_{12}H_{12}N_6O_9S$ (416.325): C, 34.62; H, 2.91; N, 20.18. Found: C, 34.50; H, 2.66; N, 20.10.

Further elution with acetone gave 168.5 mg. (9.8%) of bis[2-(2-methyl-5-nitro)imidazolyl]ethyl sulfide (VI), m.p. 158-165°, which after recrystallization from acetone had m.p. 164-170°. The pure sample melted at 173-174°; nmr (perdeuterionitromethane): δ 2.52 (s, 6H), 3.00 (t, 4H), 4.58 (t, 4H) and 7.93 ppm (s, 2H).

Anal. Calcd. for $C_{12}H_{16}N_6O_4S$ (340.360): C, 42.34; H, 4.74. Found: C, 42.45; H, 5.01.

Method B.

Compound Ia (11.70 g., 50 mmoles) and sodium thiosulfate pentahydrate (12.41 g., 50 mmoles) were mixed in methanol-water 1:1 (113 ml.). The reaction mixture was heated to reflux for 4.5 hours and evaporated to dryness. The Bunte salt X was separated from by-product sodium bromide by dissolving in a large amount of hot 2-propanol (450-500 ml.). White, light-sensitive crystalline powder precipitated on chilling (8.83 g.) and further 1.79 g. was obtained from the mother liquor, total 10.62 g. (73.5%) of sodium [2-(2′-methyl-5′-nitro)imidazolyl]ethanethiosulfate (X) m.p. 217-220°. For analysis it was once recrystallized from 2-propanol, m.p. 217-219° dec.; ir (potassium bromide): 3138 (s), 2330 (m), 1670 (m), 1539 (s), 1478 (s), 1430 (m), 1386 (s), 1370 (sm), 1270 (m), 1250 (s), 1211 (s), 1195 (s), 1043 (s) and 1031 (s) cm^{-1}; nmr (deuterium oxide): δ 2.58 (s, 3H), 3.50 (t, 2H), 4.73 (t, 2H) and 8.03 ppm (s, 1H).

Anal. Calcd. for $C_6H_8N_3NaS_2O_5$ (289.268): N, 14.53. Found: N, 14.43.

From Bunte's salt X (300 mg., 1.038 mmoles) dissolved in water (2 ml.) upon addition of 10% sulfuric acid (0.3 ml.) the white crystals of the corresponding free acid Xa precipitated (228 mg., 82.5%) m.p. 203-205° dec.; nmr (deuterium oxide): δ 2.82 (s, 3H), 3.61 (t, 2H), 4.90 (t, 2H) and 8.48 ppm (s, 1H).

Anal. Calcd. for $C_6H_9N_3O_5S_2$ (267.29): C, 26.96; H, 3.39; N, 15.72; S, 24.00. Found: C, 27.24; H, 3.49; N, 15.60; S, 24.08.

Bunte's salt X (7.22 g., 25 mmoles) was dissolved in methanol-water 1:1 (56 ml.). The flask was equiped with a Soxhlet extractor with iodine crystals (3.17 g., 12.5 mmoles) in a thimble. The reaction mixture was heated to reflux for 2.5-3 hours, cooled and a yellow-green product Va was collected (6.195 g., 78.7%) m.p. 170-180°. Recrystallization from methanol-ether or ethanol-ether gave yellow crystals of 1-(2′-thioethyl-2-methyl-5-nitroimidazole hydroiodide (Va), m.p. 180-182°; ir (potassium bromide): 3020 (w), 1532 (s), 1480 (s), 1465 (s), 1390 (m), 1360 (s), 1260 (s), 1185 (s), 823 (s) and 740 (s) cm^{-1}; nmr (pyridine-d_5): δ 2.60 (s, 3H), 3.25 (t, 2H), 4.70 (t, 2H) and 8.21 ppm (s, 1H).

Anal. Calcd. for $C_6H_{10}IN_3O_2S$ (315.13): N, 13.34; S, 10.18. Found: N, 13.26; S, 9.97.

Hydroiodide Va (1.0 g., 3.16 mmoles) was suspended in water (20 ml.) and made alkaline with 5% sodium hydroxide. Almost white crystals of the pure V were collected by filtration (580 mg., 3.10 mmoles, 98%) m.p. 117-122°.

Attempted Additions of Vinyl Ethyl Sulfone (XVII) to 2-Methyl-4(5)nitroimidazole (II).

A.

Into 2 ml. of an aqueous solution of vinyl ethyl sulfone (XVII) (containing 5.95 mmoles of XVII) 96% ethanol (24 ml.) and II (685 mg., 5.4 mmoles) were added. After stirring at 75° for two days, tlc did not show any change of the reaction mixture.

B.

Instead of ethanol, 18 ml. of glacial acetic, or the same amount of formic acid were used. No change was observed after stirring at 85° for two days.

C.

To XVII (5.95 mmoles) in water (2 ml.) II (685 mg., 5.4 mmoles) and 23 ml. of 0.1 *N* sodium acetate buffer solution, *p*H 4.25, were added. After refluxing for three days under stirring, a new spot, different from that of IV was observed. Water was removed *in vacuo* and the residue was separated by column chromatography (145 x 0.9 cm, 27 g. of silica gel) with ether-acetone (2:1 vol.) as eluent. The new substance, XXII, 116 mg. (8.7%) had m.p. 130-134°. Recrystallized from 96% ethanol melted at 139-141°; nmr (acetone-d_6): δ 1.33 (t, 3H), 2.47 (s, 3H), 3.16 (q, 2H), 3.77 (t, 2H), 4.63 (t, 2H) and 8.20 ppm (s, 1H).

Anal. Calcd. for $C_8H_{13}N_3O_4S$ (247.274): C, 38.86; H, 5.30; N, 16.99. Found: C, 38.60; H, 5.55; N, 16.75.

D.

To 2.65 ml. of an aqueous solution of XVII (7.89 mmoles), acetic anhydride was added (21.3 ml.) and II (1.0 g., 7.89 mmoles) was added with ice-cooling. The ice-bath was then removed and the reaction mixture allowed to reach room temperature. An exothermic reaction started and the temperature soon rose to 80°. Tlc showed a new spot with Rf 0.85-0.90 (in ether-acetone 3:1); while the starting compound II had Rf 0.45 and IV Rf 0.35. This compound, presumably the N^1-acetyl derivative of 2-methyl-4(5)-nitroimidazole (XXIII), was obtained as a crude product after evaporation of the solvent and XIV. The highly unstable amorphous residue exhibited the following nmr spectrum (DMSO-d_6): δ 2.40 ppm (s, 3H), 2.78 (s, 3H), and 8.83 (s, 1H); contaminated with some unacylated compound II.

[2-(2′-Methyl-5′-nitro)imidazolyl]ethanesulfonic Acid (VII).

Compound Ia (9.35 g., 40 mmoles) and sodium sulfite (7.59 g., 60 mmoles) were dissolved in a mixture of water (40 ml.) and 96% ethanol (12 ml.) at 65°. Stirring at this temperature was continued for 6.5 hours. The reaction mixture was then evaporated *in vacuo*. The residual dark-red viscous mass was very hygroscopic, and all attempts to obtain the pure substance VII and crystallize

it, failed. For characterization, the barium salt was prepared (by precipitating with barium hydroxide in water), a grey amorphous substance, decomposing above 250°.

Anal. Calcd. for $C_{12}H_{16}N_6O_{10}S_2Ba$ (605.79): Ba, 22.68. Found: Ba, 22.20.

Sodium Ethanesulfinate (XXI).

Sodium sulfite (18.1 g., 144 mmoles) was dissolved with stirring in water (87 ml.) and bromoethane (XVIII) (8.7 ml., 12.6 g., 115 mmoles) was added. The reaction mixture was vigorously stirred and refluxed. In 4-4.5 hours the b.p. of the mixture rose from 38° to 104°, indicating that all of the XVIII was consumed and the reaction completed. Water was removed *in vacuo* and the white powdered product was dried 2 hours at 105°; 29.4 g. (96% of theory, 30.5 g.) of a mixture of sodium ethanesulfonate (XIX), sodium bromide and excess sodium sulfite was obtained. The crude product was not isolated but directly used in the next step.

The mixture was suspended in dichloromethane (220 ml.) and cooled to -15°. Phosphorus pentachloride (16 g., 77 mmoles) was added portionwise during 30 minutes. Stirring at -10° to 0° was continued for 2-2.5 hours and the reaction mixture was poured into crushed ice and water. The layers were separated and the water layer extracted twice with dichloromethane (300 ml.). The combined extracts were washed twice with cold water, dried overnight at 0° (calcium chloride and sodium sulfate) and evaporated *in vacuo* (water bath maximum 30-33°) affording 12.0 g. (81.1%) of ethane-sulfochloride (XX) as a yellow oil of unpleasant odour, b.p. 84-87°/35 mm. (lit. (17) b.p. 95-98°/50 mm.). The sulfochloride XX proved to be unstable at room and elevated temperature, decomposing into ethene, sulfur dioxide and hydrogen chloride. Compound XX has to be isolated in the cold, otherwise the yield drops significantly. For the reduction to sulfinate XXI, sodium sulfite (19.0 g., 150 mmoles) was dissolved in water (60 ml.) and XX (9.65 g., 75.0 mmoles) was added portionwise. The solution was stirred for 1.5 hours at 45-55° maintaining pH 8-9 by the dropwise addition of 40% sodium hydroxide. The reaction mixture was sitrred for another 30 minutes and then the water was removed *in vacuo*. The sulfinate XXI was separated from inorganic salts by refluxing for 30 minutes with 150-200 ml. of absolute ethanol and hot filtration. This procedure was repeated twice, and the combined filtrates evaporated to dryness, yield 5.7 g. (65%) of anhydrous sodium ethanesulfinate (XXI) as white, slightly hygroscopic powder; 2880 (m), 1085 (m), 1030 (s), and 980 (s) cm^{-1}.

Vinyl Ethyl Sulfone (XVII).

Compound XI (10 ml., 9.9795 g., 94 mmoles) and potassium hydroxide pellets (10 g., 179 mmoles) were heated on an oil bath at 210-225°. The crude sulfide XV (8.026 g., 97%) distilled at b.p. 85-92°. It was diluted with ether (50 ml.) and filtered through a column of molecular sieves 4-A. The eluate was redistilled and the fraction boiling at 91-93° was taken (lit. (27) b.p. 91-93°). Pure vinyl ethyl sulfide (XV) 4.59 g. (56%) was obtained.

Compound XV (1.0 g., 11.33 mmoles) was mixed with acetone (1.2 ml.) and 30% hydrogen peroxide (1.1 ml., 11.33 mmoles) was added with ice-cooling. The reaction mixture was kept overnight at 0° and stirred at room temperature for several hours. The solvent was evaporated *in vacuo* yielding vinyl ethyl sulfoxide (XVI) (1.17 g., 100%) as a clear, colourless liquid; ir (neat): 2980 (m), 2910 (m), 1460 (s), 1420 (s), 1380 (s), 1250 (m), 1060 (s), 1030 (s) and 990 cm^{-1} (m); nmr (deuterium oxide): δ 1.23 (t, 3H), 2.92 (q, 2H), 5.96 (d, J_{trans} 16 Hz, 1H), 6.08 (d, J_{cis} 10 Hz, 1H) and 6.76 ppm (dd, 1H). For further oxidation XVI (1.17 g., 11.3 mmoles) was dissolved in water (1.3 ml.), and the same amount of 30% hydrogen peroxide (1.1 ml.) was added. After two hours stirring at 50-70° tlc showed only the spot of vinyl ethyl sulfone (XVII). This compound was always freshly prepared and used without isolation because of easy polymerization (lit. (28) b.p. 105-106°/8 mm.).

REFERENCES

(1) Part II; F. Kajfež, D. Kolbah, M. Oklobdžija, T. Fajdiga, M. M. Slamnik and V. Šunjić, *Croat. Chem. Acta*, **39**, 199 (1967).

(2) J. A. Taylor, J. R. Migliardi and H. Schach von Wittenau, *Antimicrob. Agents Chemother.*, 257 (1969).

(3) J. Frick and A. Decrisotoforo, *Therapiewoche*, 472 (1971).

(4) B. Plotho and H. Kölbl, *Wiener Med. Wochenschr.*, **40**, 707 (1971).

(5) P. G. Welling and A. N. Monro, *Arzneim.-Forsch.*, **22**, 2128 (1972).

(6) Chas. Pfizer and Co., South African Patent, 6,607,466 (1967); *Chem. Abstr.*, **71**, 3384e (1969).

(7) M. W. Miller, H. L. Howes Jr., R. V. Kasubick and A. R. English, *J. Med. Chem.*, **13**, 849 (1970).

(8) Chas. Pfizer and Co., U. S. Patent 3,376,311 (1968); *Chem. Abstr.*, **69**,52141r (1968).

(9) F. Kajfež, V. Šunjić, D. Kolbah, T. Fajdiga and M. Oklobdžija, *J. Med. Chem.*, **11**, 167 (1968).

(10) V. Šunjić, F. Kajfež, D. Kolbah and N. Blažević, *Pharmazie*, **27**, 131 (1972) (review).

(11) V. Šunjić, D. Kolbah, F. Kajfež and N. Blažević, *J. Med. Chem.*, **11**, 1264 (1968).

(12) Houben-Weyl, "Methoden in der Ortanischen Chemie", Vol. IX, Georg Thieme Verlag, Stuttgart, 1955, p. 67.

(13) K. Schank and H. Hachmann, *Ann. Chem.*, **760**, 27 (1972).

(14) K. Schank and A. Weber, *Chem. Ber.*, **105**, 2188 (1972).

(15) N. Kornblum, M. M. Kestner, S. D. Boyd and L. C. Cattran, *J. Am. Chem. Soc.*, **95**, 3356 (1973).

(16) H. G. Houlton and H. V. Tartar, *ibid.*, **60**, 544 (1938).

(17) W. Davies and J. M. Dick, *J. Chem. Soc.*, 483 (1932).

(18) J. Murakoshi, S. Ohmiya and J. Haginiwa, *Chem. Pharm. Bull.*, **20**, 609 (1972).

(19) V. D. Sheludakov, N. A. Viktorov, G. V. Rasin and V. F. Mironov, *Zh. Obshch. Khim.*, **42**, 364 (1972).

(20) V. Šunjić, F. Kajfež, D. Kolbah and P. Rems, *Bull. Sci. Conseil. Acad. RSF Yugoslavia, Sect. A*, **12**, 59 (1967).

(21) F. Kajfež, V. Šunjić, L. Klasinc and D. Marcel, *Proc. Intern. Symp. Gas Chrom. Mass Spectr.*, A. Frigerio, Ed., Tombusini, Ed., Milano 1972, p p. 206-211.

(22) J. C. Philips and M. Oku, *J. Org. Chem.*, **37**, 4479 (1972).

(23) P. H. Good, G. Jones and J. R. Phipps, *J. Org. Soc. (Perkin I)*, 2441 (1972).

(24) W. R. Kirner, *J. Am. Chem. Soc.*, **50**, 2452 (1928).

(25) T. P. Dawson, *ibid.*, **55**, 2071 (1933).

(26) K. Akagi, I. Ode and M. Murakami, *ibid.*, **78**, 4034 (1956).

(27) T. F. Doumani, U. S. Patent 2,402,878 (1942); *Chem. Abstr.*, **40**, 6496 (1946).

(28) E. A. Fehnel and M. Carmack, *J. Am. Chem. Soc.*, **71**, 237 (1949).