lized from $CHCl_3$ to yield 450 mg (90%), mp 157–160°. A mixture melting point and nmr comparison with indomethacin confirmed the structure.

Rearrangement of *endo*- and *exo*-2-(*p*-Chlorobenzoyl)-5-methoxy-1,1a,2,6b-tetrahydrocycloprop[*b*]indole-1-carboxylic Acid (39 and 14) to 1-(*p*-Chlorobenzoyl)-5-methoxyindole-3-acetic Acid. Compounds **39** and **14** were rearranged as described above. Both reactions gave a 50% yield of 1-(*p*-chlorobenzoyl)-5-methoxyindole-3-acetic acid after recrystallization from $CHCl_3$: mp 199–200°. *Anal.* ($C_{18}H_{14}ClNO_4$) C, H, N.

Acknowledgment. The authors thank Mrs. Rosa Mealy and Mr. Johnnie Nicholas for pharmacological assistance.

Supplementary Material Available. Nmr spectra for compounds **13** and **38** will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JMED-74-544.

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An Efficient and Selective Method for the Synthesis of 2-(4-Fluorophenyl)-1-(2-hydroxyethyl)-5-nitroimidazole (Flunidazole)

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The specific N-alkylation of 2-substituted 4(5)-nitroimidazoles has become a problem of significant importance because of the utility of these compounds in the treatment of protozoan infections. Generally, the 1-alkylated-2-substituted 5-nitroimidazoles are the preferred isomers because of their superior efficacy in the treatment of these infections.[1,2] Ridd and coworkers have presented a detailed analysis of the factors controlling the site of alkylation in 4(5)-nitroimidazoles and related systems,[3] and the Pfizer group has recently summarized the factors controlling the alkylation of 2-substituted 4(5)-nitroimidazoles in general.[2] Briefly stated their conclusions are: (1) alkylation under basic conditions affords 1-alkyl-4-nitroimidazoles, alkylation having occurred at the more basic nitrogen of the anion; (2) under neutral or mildly acidic conditions alkylation occurs on the unprotonated nitrogen, which is dependent on the equilibrium between the two tautomeric forms of the imidazole; and (3) in strongly acidic media the conjugate acid forms at the more nucleophilic nitrogen, thus favoring the formation of 1-alkyl-5-nitroimidazoles. Despite this information, efficient and isomer-free methods for the synthesis of 1-alkyl-2-substituted 5-nitroimidazoles are lacking.[2]

Olofson has recently addressed himself to the problem of the selective alkylation of heterocycles, including imidazoles, and has devised a sequence employing acylation, carbonium ion alkylation, and deacylation.[4] He notes that acylation is an efficient reaction and affords a high selectivity in isomer pereference, possibly due to its reversibility and, therefore, formation of the thermodynamically more stable product. However, this sequence was not applicable in our studies, as the intermediate *N*-acylnitroimidazoles failed to react with carbonium ion reagents.†

Our studies relative to the alkylation of nitroimidazoles arose out of the need to devise an efficient, isomer-free synthesis of 2-(4-fluorophenyl)-1-(2-hydroxyethyl)-5-nitroimidazole (flunidazole, **2**), which has shown appreciable antitrichomonal and antiamebic effects in man.[5]

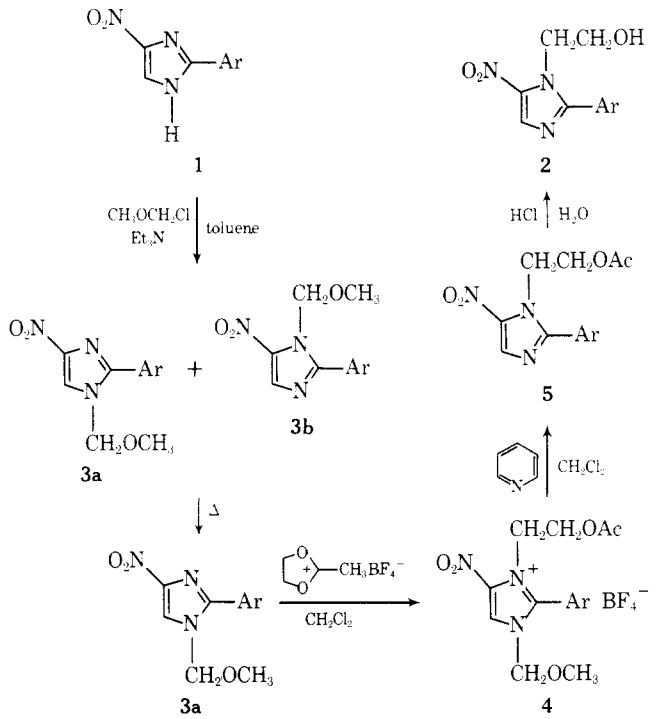
The specific problem centered about the alkylation of 2-(4-fluorophenyl)-4(5)-nitroimidazole (**1**) which can be readily prepared from either 2-(4-fluorophenyl)imidazole[5a] or 2-phenylimidazole.[6,7] The direct methylation of **1** with dimethoxycarbonium tetrafluoroborate[8] proceeds in 70–75% yield to afford the methyl analog of **2**, 2-(4-fluorophenyl)-1-methyl-5-nitroimidazole.[9] To our knowledge this represents the first reported alkylation of nitroimidazoles with onium salts. An attempt to prepare **2** (*via* acetate **5**) directly from **1** using the Meerwein reagent 2-methyl-1,3-dioxolenium tetrafluoroborate,[10] followed by acid hydrolysis, afforded a 20–30% yield of **2** along with comparable amounts of its 4-nitro isomer and unreacted starting material.†,[9] Most likely steric factors become significant during the attempted acetoxyethylation with this reagent, which are of lesser importance during the methylation with dimethoxycarbonium tetrafluoroborate. As a solution to the problem at hand we envisioned a protection–alkylation–deprotection sequence. Specifically, we wished to methoxymethylate **1** at N-1 under basic conditions, alkylate at N-3 with 2-methyl-1,3-dioxolenium tetrafluoroborate[10] to afford imidazolium salt **4**, and demethoxymethylate to afford acetate **5** which could be hydrolyzed to **2**.

The methoxymethylation of **1** was conducted in toluene at 25–30° employing an excess of triethylamine and chloromethyl methyl ether, anticipating the selective formation of **3a** *via* alkylation of the anion of **1**.[11] Compound **3a** was originally prepared by Drs. Kollonitsch and Marburg of these laboratories and used to prepare **2** by treatment with ethylene oxide–boron trifluoride etherate in a procedure less efficient than that described herein. Work-up after complete consumption of **1** afforded a 3:1 mixture of methoxymethyl compounds **3a** and **3b**, respectively, indicating that **1** and its anion alkylate competitively under the reaction conditions. Isomer assignments are based upon uv and nmr spectra. In accord with previous literature examples the methylene group of **3b** exhibited its resonance slightly downfield (0.31 ppm) of that of **3a** due to the deshielding effect of the nitro group, and the long wavelength maximum of **3a** occurred at slightly shorter wavelength than that of **3b**.[2] Although the alkylation of **1** lacked the desired specificity, **3b** could be readily isomerized to the thermodynamically more stable **3a** by refluxing the reaction mixture for 1 hr.[12] Work-up of the reaction mixture afforded pure **3a** in 97% yield, thus realizing the goal of the protection of **1** at N-1. Compound **3a** was acetoxyethylated by treatment with 2 equiv of 2-methyl-1,3-dioxolenium tetrafluoroborate in dry methylene chloride for 40 hr at reflux. Subsequent work has shown that the same sequence can be run in 1,2-dichloroethane employing a 5-hr reflux period. The resulting imidazolium salt **4** was isolated in 86% yield by filtration, water trituration to remove access Meerwein reagent, and drying and characterized in the usual manner (Scheme I). However, in the normal conversion of **1** to **2**, imidazolium salt **4** was not isolated. Rather, the reaction mixture, containing **4** and excess Meerwein reagent in methylene chloride, was treated with an excess of pyridine for 5 hr at reflux.

†E. J. J. Grabowski, *et al.*, unpublished results.

Pyridine quantitatively demethoxymethylated **4** to afford **5** and 1-methoxymethylpyridinium tetrafluoroborate and presumably reacted with excess Meerwein reagent to afford 1-(2′-acetoxyethyl)pyridinium tetrafluoroborate. No effort has been made to isolate and characterize the latter. The methylene chlroide reaction mixture was washed with water to remove the tetrafluoroborate salts and concentrated to afford crude **5**, which was hydrolyzed in dilute HCl to afford crude **2** in 92% yield based on **3a**. Recrystallization proceeded in 90% yield, thereby affording pure **2** in 80% yield based on **1**.

Scheme I



In addition to pyridine, triethylamine, ammonia, iodide ion, thiocyanate ion, and bromide ion specifically demethoxymethylated **4** to yield **5**. Hydrolysis of the reaction mixture containing **4** with aqueous HBr afforded **2** directly; however, the presence of HBF_4 had a deleterious effect on the glass reaction apparatus, and the product had to be purified from borates and silicates.

Thus, we achieved the specific objective of an efficient, isomer-free synthesis of **2**. Although we have not attempted to generalize the reaction *via* application to other nitroimidazoles or heteroaromatics, in principle it represents a potentially inexpensive and efficient procedure for the specific hydroxyethylation of these compounds at normally unfavored positions. As such, it could be superior to the established epoxide methodology. Beyond this, the sequence represents a potentially general method for the controlled alkylation of heteroaromatics employing the readily removed methoxymethyl group to direct the alkylation, followed by alkylation with the stronger alkylating agents, and deprotection. As such, it should complement the existing methods of direct alkylation of heteroaromatics and alkylation of acyl-protected heteroaromatics.

Experimental Section

Melting points were determined on a Hoover capillary melting point apparatus and are uncorrected. Uv spectra were obtained on a Cary 14 spectrometer. The nmr spectra were taken on a Varian A-60 spectrometer using TMS as an internal standard. We wish to thank Dr. A. W. Douglas and Mr. R. C. Zerfing for obtaining the nmr spectra and Mr. R. N. Boos and his associates for obtaining the elemental analysis. Indicated anlayses were correct to within 0.3% of the theoretical values. All solvents or reagents indicated as "dry" were dried at least 24 hr over molecular sieves prior to use and contained 0.01–0.02 mg of H_2O/ml as determined by Karl Fisher analysis.

2-(4-Fluorophenyl)-1-methoxymethyl-4-nitroimidazole (3a). To a stirred suspension of 2-(4-fluorophenyl)-4(5)-nitroimidazole[6,7] (24.86 g, 0.120 mol) in 248 ml of dry toluene under a N_2 atmosphere was rapidly added 12.2 g (16.8 ml, 0.120 mol) of dry triethylamine. After stirring at 25° for 15 min, 10.2 g (9.75 ml, 0.120 mol) of chloromethyl methyl ether was added dropwise over 25 min maintaining a reaction temperature of 20–25° with a cold water bath. After stirring for 3 hr, an additional 6.09 g (8.4 ml, 0.060 mol) of triethylamine was rapidly added. After stirring for 15 min 5.1 g (4.9 ml, 0.060 mol) of chloromethyl methyl ether was added dropwise over 15 min. The mixture was stirred for 1 hr at 25° and refluxed for 1 hr. The reaction mixture was concentrated at reduced pressure, slurried with 200 ml of CH_2Cl_2, and washed with 2 × 100 ml of 2.5 *N* HCl, 2 × 100 ml of 7.5 *N* NH_4OH, and 100 ml of H_2O. Drying over Na_2SO_4 was followed by concentration to about 50 ml. *n*-Hexane (200 ml) was slowly added to the stirred residue. After aging for 15 min the precipitate was filtered, washed with 40 ml of *n*-hexane, and dried at 50° (0.1 mm) to afford 29.4 g (0.117 mol, 97.4%) of 2-(4-fluorophenyl)-1-methoxymethyl-4-nitroimidazole as a tan powder: mp 113–115°; uv max (0.1 *N* HCl in CH_3OH) 305 nm (ε 7655), 230 (13,050); nmr ($CDCl_3$) δ 5.34 (s, 2, $-OCH_2N=$). *Anal.* ($C_{11}H_{10}FN_3O_3$) C, H, N.

2-(4-Fluorophenyl)-1-methoxymethyl-5-nitroimidazole (3b). The above reaction was repeated on a 0.100-mol scale, eliminating the 1-hr toluene reflux. Upon completion of the addition and aging periods the reaction mixture was diluted with 100 ml of CH_2Cl_2, washed with 2 × 100 ml of 2.5 *N* HCl, 2 × 100 ml of 7.5 *N* NH_4OH, and 100 ml of H_2O, dried over Na_2SO_4, and concentrated to about 40 ml. *n*-Hexane (200 ml) was slowly added to the residue and the resulting precipitate was aged at 0° for 3 hr. Filtration, washing with 100 ml of *n*-hexane, and drying at 50° (0.1 mm) afforded 21.53 g (0.086 mol, 86%) of a 3:1 mixture of **3a** and **3b**, respectively, as indicated by nmr (see below). A sample of pure **3b** was obtained as follows. The mother liquor which yielded the above mixture was taken to dryness affording 1.30 g of an orange solid. This was recrystallized from 10 ml of 2-propanol using 0.26 g of Darco G-60 to afford 0.91 g of 2-(4-fluorophenyl)-1-methoxymethyl-5-nitroimidazole (**3b**): mp 78–80°; uv max (0.1 *N* HCl in CH_3OH) 318 nm (ε 7760), 288 (5570), 256 (13,250); nmr ($CHCl_3$) δ 5.65 (s, 2, $-OCH_2N=$). This material was identical with the minor component present in the above mixture as indicated by nmr. *Anal.* ($C_{11}H_{10}FN_3O_3$) C, H, N.

2-(4-Fluorophenyl)-1-(2-hydroxyethyl)-5-nitroimidazole (2). A special three-necked flask was designed containing a filter disk built into one of the necks. A 1-atm bubbler designed to permit nitrogen flow to the system when it was below 1 atm was connected. Filtrations were performed within the flask by applying vacuum at the neck equipped with the filter disk with the flask appropriately tipped. With this apparatus moisture was rigorously excluded from the system.

To a vigorously stirred solution of 15.0 g (0.110 mol) of 2-ethoxy-2-methyl-1,3-dioxolane in 27.5 ml of dry CH_2Cl_2 at 5° under N_2 was added dropwise 20.8 g (0.146 mol) of boron trifluoride etherate over 30 min maintaining a temperature of 5–10°. The resulting precipitate of 2-methyl-1,3-dioxolenium tetrafluoroborate was filtered *in situ* as described above and washed with 4 × 60 ml of dry CH_2Cl_2. The washings are required to remove triethylborate, a reaction by-product which during the subsequent step can lead to an ethylating species. To the filtered salt was added 55 ml of dry CH_2Cl_2 followed by the rapid addition of 12.56 g (0.050 mol) of 2-(4-fluorophenyl)-1-methoxymethyl-4-nitroimidazole (**3a**) in 65 ml of dry CH_2Cl_2. The resulting mixture was stirred vigorously and refluxed for 40 hr. Dry pyridine (13 g, 0.17 mol) was then added and the reflux was continued for an additional 5 hr. Water (100 ml) was added and the mixture shaken. After separation of the CH_2Cl_2 layer, the aqueous layer was extracted with 2 × 50 ml of CH_2Cl_2. The combined CH_2Cl_2 solutions were washed with 50 ml of H_2O and concentrated to remove the CH_2Cl_2. The remaining oil, which was essentially pure **5** and crystallized on standing, was dissolved in 144 ml of 2.5 *N* HCl, refluxed for 50 min, and adjusted to pH 8.5 with 62 ml of 2.5 NaOH at 20–25°. The resulting precipitate was aged at 0° for 1 hr, filtered, washed with 3 × 20 ml of H_2O, and dried at 50° (0.1 mm) to afford 11.6 g (0.0462 mol,

92.4%) of crude **2**: mp 162–164°. This was dissolved in 180 ml of hot acetone, treated with 1.16 g of Darco G-60, filtered, and concentrated to a volume of 100 ml. While maintained at 55°, 100 ml of 1 *N* NH_4OH was added dropwise over 10 min. The NH_4OH serves as a base for any regenerated 1 and retains it in solution as the anion. After standing for 30 min at 25° and 30 min at 0° the resulting crystalline yellow solid was filtered, washed with 50 ml of 1:1 1 *N* NH_4OH–acetone and 300 ml of H_2O, and dried at 50° (0.1 mm) to afford 10.30 g (0.0412 mol, 89%, 82.4% based on **3a**) of **2**: mp 166.5–167.5°. *Anal.* ($C_{11}H_{10}FN_3O_3$) C, H, N, F. This material was identical in every respect with that previously reported.[5]

3-(2-Acetoxyethyl)-2-(4-fluorophenyl)-1-methoxymethyl-4-nitroimidazolium Tetrafluoroborate (4). The reagents were prepared and combined in the quantities indicated in the previous experiment and the reaction mixture was refluxed for 40 hr. The resulting precipitate was filtered, washed with 50 ml of CH_2Cl_2, slurried with 100 ml of H_2O, refiltered, washed with 25 ml of H_2O, and dried at 50° (0.1 mm) to afford 17.3 g (81.6%) of imidazolium salt **4**: mp 134–136°. *Anal.* ($C_{15}H_{17}BF_3N_3O_5$) C, H, N.

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Synthesis and Biological Properties of 5-Aryl-4*H*-1,2,4-thiadiazine 1,1-Dioxides†

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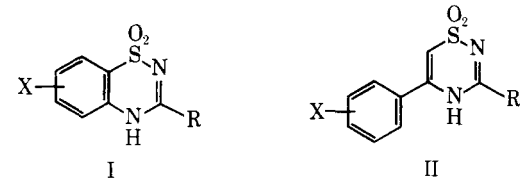
1,2,4-Benzothiadiazine 1,1-dioxides (I) are well-known diuretic and/or antihypertensive agents.[1-3] However, examples of nonfused, fully unsaturated 1,2,4-thiadiazine 1,1-dioxides have not been reported.[4] We have now synthesized 5-aryl-4*H*-1,2,4-thiadiazine 1,1-dioxides of type II and tested them for antihypertensive and diuretic activity.

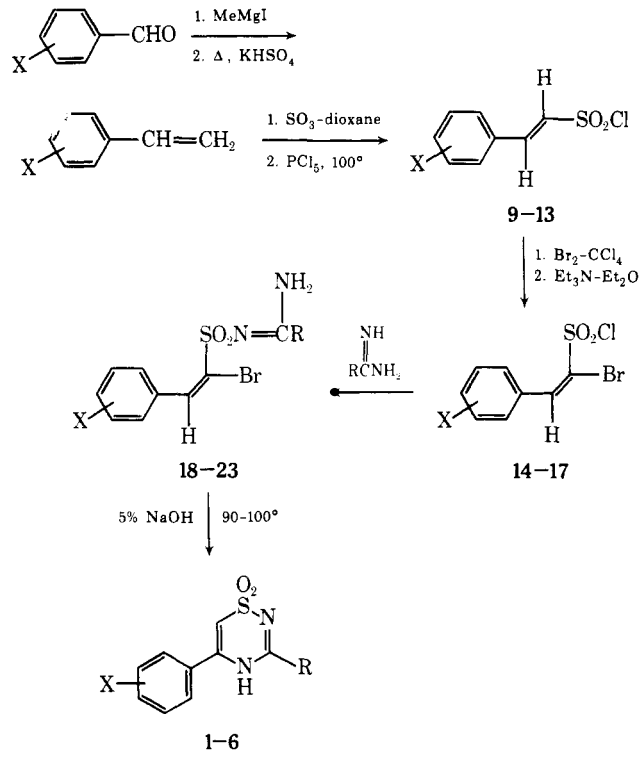
Chemistry. The 5-aryl-4*H*-1,2,4-thiadiazine 1,1-dioxides in Table I were prepared by the route shown in Scheme I. Styrene is available commercially, but chlorinated styrenes were obtained from the corresponding benzaldehydes by the method of Brooks.[5] The styrenes were converted to *trans*-styrylsulfonyl chlorides (Table II) by the method of Bordwell, *et al.*[6] The nitro derivatives **12** and **13** were readily prepared by nitration of the unsubstituted compound **9** according to the procedure of Bordwell, *et al.*[7] We assign the trans configuration to these compounds on the basis of the coupling constants of their vinyl protons in the nmr spectra ($J \sim 15.5$ Hz).



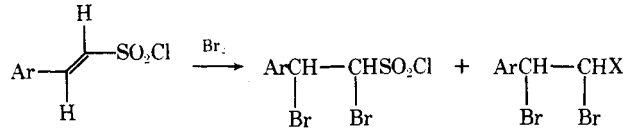
I II

chlorothiazide: R = H; X = 6-Cl, 7-SO_2NH_2
diazoxide: R = Me; X = 7-Cl

Scheme I



Compounds **14–17** in Table II were prepared by bromination followed by dehydrobromination of the corresponding styrylsulfonyl chlorides as described by Rondestvedt.[8] The bromination reaction is often complicated by the formation of products which have lost the sulfonyl group. These products appear to be III based on the nmr and mass spectra of the product mixtures and are probably formed *via* a free-radical process. The 4-nitro derivative **17** was obtained by nitration of **14**. These α-bromostyrylsulfonyl chlorides probably have the *E* configuration, as suggested by Rondestvedt,[8] since the parent compound could not be dehydrobrominated to the acetylenic sulfonyl chloride and, under forcing conditions, lost the sulfonyl group.



III, X = Br or Cl

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