

Table II. Local Anesthetic Potency and Toxicity

Compd	Corneal anesthesia ^a		Sciatic nerve block <i>in vitro</i> ^b		LD ₅₀ , ^c iv	
	Duration min ± SE	Relative activity	Depression of action potential, % ± SE	Relative activity	mg/kg	Relative toxicity
(R)-(+)-1	15.4 ± 1.8	1.0	96 ± 3	1.0	8	1.0
(S)-(-)-1	8.4 ± 0.9	0.5	44 ± 1	0.5	20	0.4
(R)-(+)-2	14.2 ± 0.9	0.9	87 ± 3	0.9	11	0.7
(S)-(-)-2	1.8 ± 0.6	0.1	50 ± 4	0.5	19	0.4
(R)-(+)-Bupivacaine	14.6 ± 1.8	1.0	87 ± 6	0.9	6	1.3
(S)-(-)-Bupivacaine	11.5 ± 1.5	0.7	48 ± 7	0.5	10	0.8

^aRabbit, 0.25%, 0.25 ml applied for 0.5 min, *N* = 6. ^bFrog, 0.1 mM, equilibrium block, *N* = 4. ^cMice.

scribed for the (+) enantiomer,⁷ mp 192–193.5° (from EtOH–H₂O), [α]_D²⁰ –105.1° (*c* 1.02, 95% EtOH). Anal. (C₁₀H₁₀ClNO₂) C, H, N.

Resolution of (±)-*N*-Butyl-3-hydroxypiperidine (3). To a solution of 26.1 g (0.083 mole) of (+)-4-chlorotartronic acid⁷ in warm 95% EtOH (175 ml) (±)-3 (25 g, 0.166 mole) was added. The mixt was kept at room temp for 24 hr, and the formed salt was collected. Two recrystns from 95% EtOH and seeding with crystals from a previous experiment afforded 13.0 g of product, mp 151–153°, [α]_D²⁰ +63.5° (*c* 1.02, H₂O).

The optically active salt (5.8 g) was decomposed with 5 *N* NaOH, and the amino alcohol was extracted with Et₂O. After drying (Na₂SO₄) and evaporation of the solvent, 2.0 g of (+)-3 was obtained, [α]_D²⁰ +4.0° (*c* 1.15, EtOH).

Treatment of (±)-3 with (–)-4-chlorotartronic acid yielded similarly the enantiomeric salt, mp 151.5–153.5°, [α]_D²⁰ –63.7° (*c* 1.10, H₂O). Decomposition of the salt yielded (–)-3, [α]_D²⁰ –4.3° (*c* 1.38, EtOH).

Resolution of (±)-3-Hydroxypiperidine. (±)-3-Hydroxypiperidine (5.0 g, 0.05 mole) was treated with (–)-4-chlorotartronic acid (6.5 g, 0.025 mole) in 95% EtOH as described for (±)-3. The salt obtained was recrystd twice from 95% EtOH affording 4.2 g of product, mp 152–153°, [α]_D²⁰ –77.6° (*c* 0.75, H₂O). The salt was stirred in a mixture of MeOH–PhMe (7:3) containing equivalent amounts of K₂CO₃. After filtrn and evapn, (S)-(-)-3-hydroxypiperidine was obtd, [α]_D²⁰ –8.0° (*c* 1.32, MeOH), lit.⁸ [α]_D²⁰ –7.5° (*c* 2.0, MeOH).

(S)-(+)-*N*-Butyl-3-hydroxypiperidine [(S)-(+)-3]. (S)-(-)-3-Hydroxypiperidine (0.5 g, 5 mmoles), BuI (0.5 g, 6 mmoles), and K₂CO₃ (0.7 g, 5 mmoles) were mixed in BuOH (5 ml) and stirred at 80° for 5 hr. After filtration, evapn, and trituration with Et₂O, followed by filtration and evapn, 0.42 g (54%) of (S)-(+)-3 was obtd, [α]_D²⁰ +4.2° (*c* 1.0, EtOH). Ir and tlc data were identical with those shown by (+)-3 prep'd by resoln of (±)-3.

Preparation of the Enantiomers of 1 and 2. The enantiomers of 1 and 2 were prepared from (+)-3 and (–)-3 and the appropriate isocyanate by the method described for the racemates.¹ Physical data for the optical isomers are given in Table I. When equivalent amounts of the appropriate pair of enantiomers were mixed and recrystd from ligroin, the observed mp were identical with, and did not depress, the mp of the racemic compounds. The ir spectra were also identical.

Acknowledgment. The enantiomers of bupivacaine were made available through the courtesy of Dr. G. Åberg, AB Bofors Nobel-Pharma, Mölndal, Sweden.

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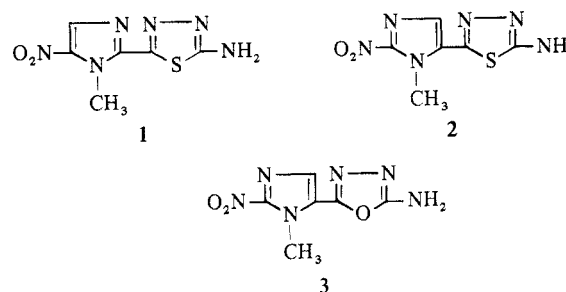
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Nitroheterocyclic Antimicrobial Agents. 1-Methyl-2-nitro-5-imidazolyl Derivatives

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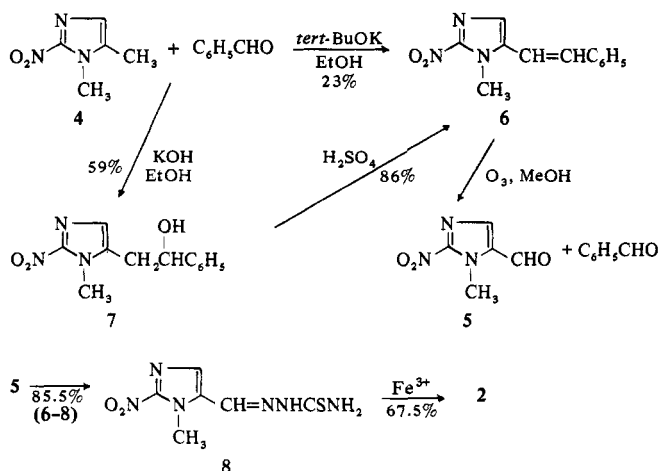
Since the discovery of the broad-spectrum antimicrobial activity of 2-amino-5-(1-methyl-5-nitro-2-imidazolyl)-1,3,4-thiadiazole (1),¹ a comparison of its activity with that of the corresponding 2-nitro isomer (2) was of interest, especially in view of the high antiprotozoal activities reported for both 5-nitro- and 2-nitroimidazoles.^{2,3} In this report, the synthesis and antimicrobial activity of 2 and its amino-oxadiazole analog (3) are described.



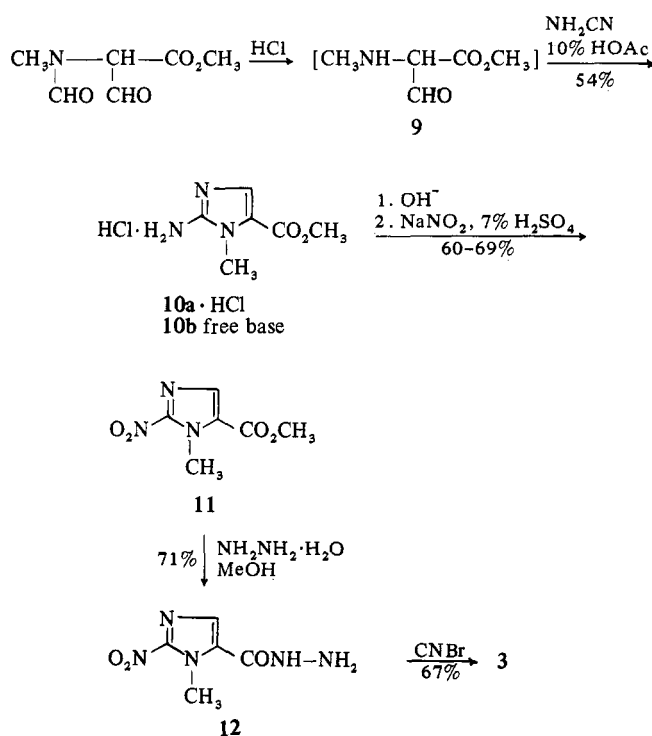
1,5-Dimethyl-2-nitroimidazole (4)³ appeared to be a potential intermediate for 1-methyl-2-nitroimidazole-5-carboxaldehyde (5). Probing experiments quickly revealed that oxidation of 4 to 5 with SeO₂ or CrO₃ proceeded only with considerable decomposition and that treatment of 4 with BuONO–HCl did not give the oxime of 5. Condensation of 4 with benzaldehyde could be accomplished by using an excess of *tert*-BuOK and benzaldehyde to afford 6 in low yield. However, in subsequent experiments, the yield of 6 was improved by using a two-step synthesis† which involved addition of 4 to benzaldehyde in the presence of a catalytic amount of KOH in EtOH to give 7, which was then dehydrated with H₂SO₄ to give 6. The benzylidene derivative was easily ozonized to 5, which was converted to the thiosemicarbazone 8. The latter was oxidatively cyclized to give 2.

A second approach was based on the method of imidazole

†We thank Drs. P. Miller and I. Starer of the Organic Chemicals Division (Bound Brook, N. J.) for providing information on this method, which they developed for the 5-nitroimidazole series.



synthesis of Lancini and coworkers.³ This involved condensation of C-formylated sarcosine ester (9) with cyanamide, which proceeded satisfactorily to give 54% of 10. Compound 10 was converted to the free base and then diazotized in a large excess of NaNO₂ with 7% H₂SO₄ in the absence of a catalyst⁴ to afford 60–69% yields of the nitroester (11). Subsequently, 11 was converted to the hydrazide (12), which was allowed to react with CNBr to give 3.



Biological Activity. Compounds 2 and 3 were tested *in vivo* orally against *Salmonella gallinarum* in chicks and *Staphylococcus aureus* (Smith), *Escherichia coli*, and *Trichomonas vaginalis* in mice. Compound 2 was inactive against these organisms. In contrast, 3 saved 5/5 mice at 64 mg/kg and 3/10 at 32 mg/kg (single oral tubing, SOT) in the *E. coli* 311 test. At these levels 1 saved 5/5 and 8/10 mice. Furthermore, 3 was slightly active vs. *Staph. aureus* at 128 mg/kg (SOT 2/5 survival) and *T. vaginalis* at 100 mg/kg, but inactive vs. *S. gallinarum* at 0.025% diet concentration. At these levels 1 is highly effective against the aforementioned infections.

Thus, these 2-nitroimidazoles are less interesting antimicrobial agents than the corresponding 5-nitroimidazoles.

As the 2-nitro group is expected to reduce the basicity of the imidazole nitrogen (position 3) to a greater extent than does the 5-nitro group,⁵ the electronic effect may be important in decreasing the antimicrobial activity of these isomeric compounds.

Experimental Section[‡]

Methyl 2-Amino-1-methyl-5-imidazolecarboxylate (10b). A solution of 58.38 g (0.367 mole) of *N*-formyl-*C*-formyl methyl sarcosinate[§] in 61 ml (0.734 mole) of concentrated HCl and 400 ml of MeOH was refluxed for 0.5 hr. The solution was evaporated to dryness *in vacuo*, and the residual oil was dissolved in 10% aqueous HOAc and heated on a steam bath for 0.5 hr with 60.3 g (0.735 mole) of NaOAc and 30.8 g (0.734 mole) of NH₂CN. After cooling, the mixture was filtered and the filtrate was acidified to pH 1 with concentrated HCl and evaporated to dryness *in vacuo*. The residue was stirred in MeOH, the mixture was filtered to remove NaCl, and the filtrate was evaporated to dryness to afford crystals and an oil. Addition of Me₂CO and traces of MeOH solubilized the oil and the crystals were collected and washed with Me₂CO–MeOH (trace) to give 39 g (54%) of product (10a); mp 198–202° dec; nmr (D₂O–1% DSS) τ 2.28 (s, 1H, imidazole H), 6.06, 6.26 (2 s, 6H, N-CH₃ and CO₂Me). A sample which was recrystallized from EtOH melted at 199–200° dec. *Anal.* (C₆H₁₀N₃O₂Cl) C, H, N, Cl.

The free base was obtained as a precipitate by adding solid K₂CO₃ to 39 g of the salt in 200 ml of H₂O. The amine was collected and washed with H₂O to afford 25.48 g. The analytical sample, mp 175–176.5°, was recrystallized from CHCl₃. *Anal.* (C₆H₉N₃O₂) C, H, N.

Methyl 1-Methyl-2-nitro-5-imidazolecarboxylate (11). A suspension of 12.05 g (0.0776 mole) of amine in 435 ml of H₂O containing 109 g (1.57 mole) of NaNO₂ at 0 to –5° was treated with 545 ml of 7% H₂SO₄ by dropwise addition. After completion of the addition, the cooling bath was removed and stirring was continued for 2 hr. The mixture was extracted with CHCl₃ (6 × 100-ml volumes) and the extracts were dried (MgSO₄) and evaporated to dryness *in vacuo* to afford 15.75 g of oil. The oil was stirred in 500 ml of Et₂O, and the soluble portion was filtered and evaporated to dryness to give pale yellow crystals, mp 57–64°. After washing with cold H₂O, 8.42 g, mp 63–65° (slightly turbid), remained. The Et₂O-insoluble resin solidified on standing and trituration with CHCl₃ gave 1.38 g of an insoluble, yellow solid, mp 186–188° dec; mass spectral analysis indicated this material was probably a mixture with *m/e* 294 and 308. The CHCl₃ filtrate was evaporated to dryness and additional nitroester was recovered. This gave 1.1 g of product, mp 61–63.5°, after washing with cold H₂O and a crude yield of 66%. A sample, which was recrystallized twice from Et₂O–hexane, melted at 63–65°. *Anal.* (C₆H₉N₃O₄) C, H, N.

1-Methyl-2-nitro-5-imidazolecarboxylic Acid Hydrazide (12). A solution of 9 g (0.0586 mole) of the nitroester in 150 ml of MeOH was cooled to 0° and 4.87 g (0.0973 mole) of NH₂NH₂·H₂O in 50 ml of MeOH was added. After 1 hr at 0°, the mixture was stirred at room temperature for 4 hr and then evaporated to dryness. The residue was triturated with H₂O, and the yellow-brown solid collected. Recrystallization from MeOH afforded 4.87 g of pale yellow crystals, mp 141–143°. Concentration of the MeOH mother liquor gave an additional 0.57 g, mp 138–144°, while concentration of the initial H₂O wash at room temperature gave 0.95 g, mp 137–141° dec. A sample, which was recrystallized twice from MeOH, melted at 141–144° dec. *Anal.* (C₆H₉N₃O₄) C, H, N.

2-Amino-5-(1-methyl-2-nitro-5-imidazolyl)-1,3,4-oxadiazole (3). The hydrazide (3.57 g or 0.019 mole) was dissolved in 75 ml of hot MeOH, and the solution was cooled to near room temperature before 2.25 g (0.0212 mole) of CNBr was added. The mixture was refluxed for 0.5 hr, evaporated to dryness, and the yellow-orange residue was stirred in H₂O and collected to give 2.13 g (67.4%), mp 258–259° dec. Recrystallization from 95% EtOH gave an analytical sample: mp 257–259°; nmr (DMSO-*d*₆) τ 2.42 (s, 1H, imidazole H), 2.47

[‡]Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Ir spectra were taken on a Perkin-Elmer Model 137 spectrophotometer; nmr spectra were taken on a Varian A-60 instrument (Me₄Si). Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Where analyses are indicated only by symbols of the elements, analytical results obtained for the elements were within $\pm 0.4\%$ of the theoretical values.

[§]We thank Dr. M. Martell (Lederle Laboratories) for furnishing the initial sample, which was prepared by the method of Jones.⁶

(broad s, 2H, -NH₂), 5.72 (s, 3H, N-CH₃) for a crude sample. *Anal.* (C₆H₆N₆O₃) C, H, N.

1-Methyl-2-nitro- α -phenyl-5-imidazoleethanol (7). A mixture of 1.7 g (0.012 mole) of 1,5-dimethyl-2-nitroimidazole (4)⁷ and 1.51 g (0.014 mole) of benzaldehyde in 6.7 g of ethanolic KOH (0.3 g of KOH/25 ml of EtOH) was stirred at room temperature under N₂ atmosphere for 22.5 hr. The mixture was evaporated to dryness *in vacuo* to afford an oil, which was mixed with ca. 15 ml of H₂O and extracted with CHCl₃ (5 \times 10 ml). The extracts were dried (MgSO₄) and evaporated to dryness to give an oil. Water was added to the oil, and benzaldehyde was removed by vacuum steam distillation on a rotary evaporator. Ether was added to the residue and an insoluble, yellow solid was obtained. This was collected and washed with Et₂O to afford 1 g of product. Evaporation of the mother liquor gave 1.7 g of semisolid which contained mostly adduct and some 4. Both fractions were later dehydrated separately to the benzylidene derivative 6. From an initial run, crude product, mp 111–115°, was recrystallized from Me₂CO–hexane and then from EtOAc to afford crystals melting at 120–121.5°. *Anal.* (C₁₂H₁₃N₃O₂) H, N; C: calcd, 58.29; found, 58.89.

1-Methyl-2-nitro-5-styrylimidazole (6). The adduct (7) (1.18 g or 47.8 mmoles) was added to a stirred mixture of 3.3 ml of HOAc and 1.1 ml of concentrated H₂SO₄ at room temperature. The mixture was heated at 110° for 20 min in an oil bath, cooled, and poured on ice to give a yellow solid which was collected to give 0.943 g (86%), mp 167–170°. A sample, which was recrystallized twice from Me₂CO–95% EtOH, melted at 170.5–171.5°. *Anal.* (C₁₂H₁₁N₃O₂) C, H, N.

1-Methyl-2-nitro-5-imidazolecarboxaldehyde Thiosemicarbazone (8). Compound 6 (1.04 g or 4.55 mmoles) was stirred heterogeneously in 40 ml of MeOH at 10° and O₃ was introduced *via* a capillary tube from a generator (Welsbach Corp., 0.081 mole/hr in O₂ stream) until a clear solution was obtained (8 min). After 15 min of additional stirring, 0.431 g (2.27 mmoles) of Na₂S₂O₅ in 5 ml of H₂O was added at below 15°, and, after 10 min, 10 ml of H₂O was added, and the mixture was evaporated to near dryness on a rotary evaporator at ca. 60–75° to give a yellow paste. An additional 20 ml of H₂O was added and the mixture was concentrated *in vacuo* until the odor of benzaldehyde was not noticeable. Subsequently, 0.42 g (4.62 mole) of thiosemicarbazide was added, and the mixture was heated on a steam bath for 40 min. After cooling, the yellow product was collected and washed with H₂O to afford 0.89 g (85.5%), mp 277° dec. A sample, which was recrystallized from a large volume of Me₂CO–EtOH, melted at 276° dec; ir 1590 cm⁻¹ (mineral oil mull). *Anal.* (C₆H₆N₆SO₂) H, N, S; C: calcd, 31.58; found, 32.03.

2-Amino-5-(1-methyl-2-nitro-5-imidazolyl)-1,3,4-thiadiazole (2). The thiosemicarbazone (8) (1.02 g or 4.47 mmoles) was added to a solution of 3.72 g (17.9 mmoles) of FeCl₃⁸ in 21 ml of H₂O and ca. 2–3 ml of EtOH was added to facilitate wetting of the crystals. After 1.5 hr at 80–85°, the mixture was cooled to room temperature and the yellow-orange crystals were collected and washed with H₂O. The yield was 0.684 g (67.5%), mp 260–261°. A sample was recrystallized from EtOH to give mp 263.5° dec; ir 3450, 3350, 3125, 1660 cm⁻¹ (mineral oil mull)—comparable high frequency bands were also present in the spectrum of 1. *Anal.* (C₆H₆N₆O₂S) C, H, N, S.

Acknowledgment. We wish to thank Dr. G. A. Kemp and staff for antibacterial assays, Mr. G. S. Redin and staff (Lederle Laboratories) for their antibacterial assays, and Dr. E. Burden and staff (Lederle Laboratories) for the *T. vaginalis* assays.

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Potential Antitumor Agents. 2.

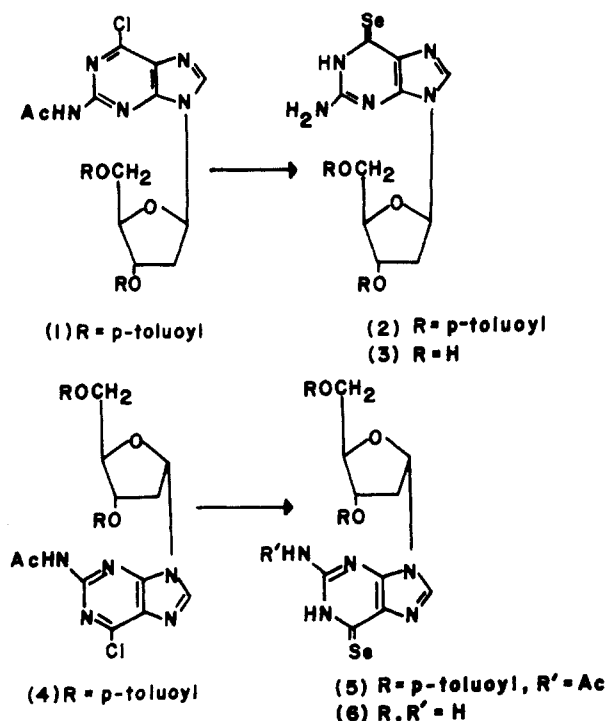
α - and β -2'-Deoxy-6-selenoguanosine and Related Compounds[†]

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6-Selenoguanine and 6-selenoguanosine were found to have a greater inhibitory effect than either thioguanine or its riboside in Sarcoma 180 ascites cells.^{1–3} 6-Selenoguanosine 5'-monophosphate behaves like 6-thioguanosine 5'-monophosphate as a potent competitive inhibitor of guanylate kinase, with inhibition constants of $(5.0\text{--}7.0) \times 10^{-5}M$ and $6.0 \times 10^{-5}M$, respectively.⁴ These results prompted the synthesis of α - and β -2'-deoxy-6-selenoguanosine (3 and 6) for similar biological studies. We now wish to report a convenient two-step synthesis of α - and β -2'-deoxy-6-selenoguanosine (Scheme I) by a modification of the procedure of

Scheme I



Iwamoto, *et al.*⁵ The reaction of 2-acetamido-6-chloro-9-(2'-deoxy-3',5'-di-O-p-toluoyl- β -D-erythro-pentofuranosyl)-9H-purine (1) with alcoholic NaOMe and hydrogen selenide required a long period of 3 days at room temperature because of the low solubility of this compound in MeOH. During this period the *N*-acetyl group was removed, and the partially protected precursor 2 of β -2'-deoxy-6-selenoguanosine (3) was obtained in 75% yield. However, the reaction of the α -D anomer 4 required only a short period of time (80 min) to give the protected precursor 5 of α -2'-deoxy-6-selenoguanosine (6) in 67% yield.

Treatment of compounds 2 or 5 with methanolic NaOMe gave β -2'-deoxy-6-selenoguanosine (3) and α -2'-deoxy-6-selenoguanosine (6) in 54 and 70% yields, respectively.

β - and α -2'-deoxy-6-selenoguanosine (3 and 6) are unstable in aqueous solution, with the half-life of the 360-nm peak in H₂O at room temperature about 24 hr.

[†]This work has been supported by Grant T-536 from the American Cancer Society, and Grants 16538-01 and CA 12591-01A1 from the United States Public Health Service.