107600-00-0; 12, 134458-54-1; 13, 134527-85-8; 14, 134527-86-9; 15, 134458-55-2; 16, 107599-97-3; 17, 134458-56-3; 18, 134458-57-4; 19, 134458-58-5; 20, 134458-59-6; 21, 134458-60-9; 22, 134458-61-0; 23, 97920-16-6; 24, 134458-62-1; 25, 134485-18-0; 26, 134458-63-2; I, 112190-15-5; II, 112190-24-6; III, 134485-19-1; IV, 134483-83-3; V, 134458-74-5; VI, 134458-75-6; VII, 107600-09-9; VIII, 134527-87-0; IX, 134623-15-7; X, 107600-10-2; XI, 112190-16-6; XII, 112190-17-7; XIII, 134458-76-7; XIV, 134458-77-8; XV, 134458-78-9; XVI, 134458-79-0; Ph_3PCHCO_2Et, 1099-45-2; *i*-BuMgBr, 926-62-5; Noa-His(Boc)-OH, 134458-73-4; protease, 9001-92-7.

2-Chloro-1-(2,4-dichlorophenyl)-3-(1*H*-imidazol-1-yl)-2-phenylpropan-1-one Hydrochloride, a Novel, Nonmutagenic Antibacterial with Specific Activity against Anaerobic Bacteria

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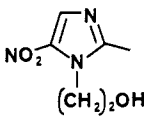
1-(2,4-Dichlorophenyl)-2-phenylpropen-1-one (2) is identified as a potent antibacterial agent. A compound, 2-chloro-1-(2,4-dichlorophenyl)-3-(1*H*-imidazol-1-yl)-2-phenylpropan-1-one (5) has been designed with the intention of its acting as a pro-drug, liberating the lethal species 2 specifically within the target anaerobic bacterial cell following bioreduction by bacterial ferredoxin or related electron transfer proteins. The synthesis and biological activity of 5 is described and compared with the activities of the analogous α-bromo ketone 6 and α-fluoro ketone 7. Synthesis of 6, 7, and the corresponding α-hydroxy ketone 11 is also described.

Anaerobic bacteria are accepted as a major cause of infection and are particularly important in postoperative sepsis following surgery of either the gastrointestinal or genitourinary tracts. For the prophylaxis and therapy of anaerobic sepsis, nitroimidazoles such as metronidazole 1 have been shown to be of considerable benefit.[1-3]



(1)

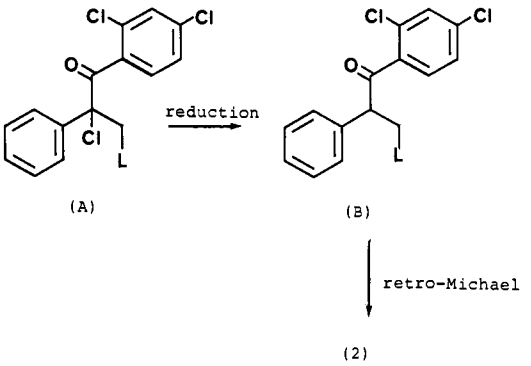
Anaerobic bacteria also play a significant role in periodontal disease. As in postoperative sepsis, nitroimidazoles have been shown to be effective,[4,5] but their usage has not yet gained as wide acceptance. One possible explanation is that metronidazole is reported to be mutagenic[6] as determined in the Ames test.[7]

It is therefore anticipated that a novel, nonmutagenic specific antianaerobe would be of considerable interest, not only in the treatment and prophylaxis of postoperative sepsis, but also in the treatment of periodontal disease.

The mode of action of metronidazole results in a remarkable specificity for anaerobic organisms. Metronidazole is a precursor of lethal intermediates (as yet unidentified) which are generated via specific bioreduction by highly reducing ferredoxins or electron-transfer proteins unique to anaerobic bacteria and some protozoa.[8-12] The absence of such reducing systems in aerobic bacteria and, more importantly, within the mammalian host ensures that such lethal species are generated specifically within the target anaerobe.

For the design of a novel agent with the same level of specificity it is desirable to utilize the uniqueness of these bacterial ferredoxins. Conceptually this involves the choice of a suitable lethal intermediate which is generated only under such reducing conditions. Other groups[13] have screened potentially bioreducible compounds in the search for specific antianaerobe activity but we have chosen to take a compound with demonstrable antibacterial activity and seek to enhance its specificity by ensuring that it is

Scheme I



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‡ Department of Biology.

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0022-2623/91/1834-2356$02.50/0

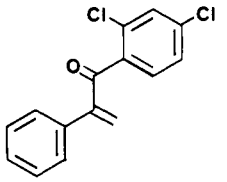
Table I. In Vitro Activity of Test Compounds against a Range of Anaerobic Bacteria[a]

organism	MIC, μg/mL						
	5	6	7	2	9	11	*MZ*
Bacteroides fragilis NCTC 10581	<0.8	<0.8	50	<0.8	<0.8	50	<0.8
Bacteroides fragilis NCTC 9343	<0.8	<0.8	50	<0.8	<0.8	>100	<0.8
Bacteroides fragilis NCTC 9344	<0.8	<0.8	50	<0.8	<0.8	>100	<0.8
Bacteroides fragilis MZ-R	<0.8	<0.8	50	<0.8	<0.8	>100	6.2
Bacteroides fragilis WSI	<0.8	<0.8	50	<0.8	<0.8	>100	1.5
Clostridium perfringens NCTC 523	<0.8	<0.8	3.1	<0.8	<0.8	12.5	<0.8
Clostridium perfringens NCTC 8237	<0.8	<0.8	3.1	<0.8	<0.8	25	<0.8
Fusobacterium necrophorum ATCC 11295	<0.8	<0.8	25	<0.8	<0.8	>100	<0.8
Peptococcus magnus	<0.8	1.5	25	<0.8	<0.8	>100	<0.8
Peptococcus prevotti	<0.8	1.5	6.2	<0.8	<0.8	12.5	1.5
Peptostreptococcus anaerobis	<0.8	1.5	25	<0.8	<0.8	50	<0.8
Propionibacterium acnes NCTC 737	<0.8	<0.8	25	<0.8	<0.8	100	>100
Propionibacterium acnes NCTC 7337	<0.8	<0.8	25	<0.8	<0.8	50	>100

[a] For methodology see Experimental Section.

liberated specifically within the target cell following bioreduction.

In the course of earlier investigations[14] into the discovery of potential new antianaerobe agents we observed that the α,β-unsaturated ketone **2** was a potent antibacterial agent.

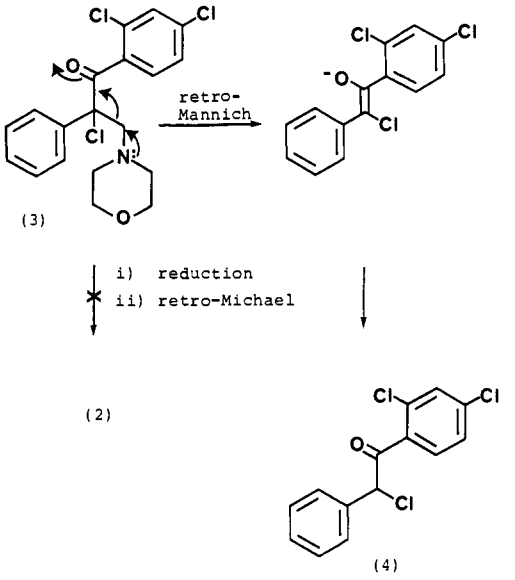


(2)

The antibacterial activity of α,β-unsaturated carbonyl compounds in general is well known.[15] Other workers[16] have recently reported similar α,β-unsaturated ketones to have in vitro activity against fungi. The impressive in vitro activity of **2** against a range of anaerobic bacteria is shown in Table I. However, this compound, which was isolable only as a gum, deteriorated on standing overnight at 5 °C, affording a complex mixture of higher molecular weight materials which were not characterized. This evident instability and the chemical ability of **2** to function as a reactive electrophile suggests it may be a ubiquitous alkylating agent and therefore not a suitable drug molecule to be pursued in its own right. However if this molecule could be unmasked specifically within the anaerobic organism it could prove to be an excellent antianaerobe.

A search of the literature for suitable molecules with reduction potential similar to that of metronidazole revealed phenacyl chloride to be in this category (see Table III). Extrapolation of this observation into a workable mechanistic sequence for our purpose is shown in Scheme

Scheme II



I. Reduction of the α-chloro ketone A to generate B is designed to be possible only within the target organism. Assuming that an appropriate leaving group L is also chosen, the ketone B is then capable of a retro-Michael reaction to liberate the reactive electrophile **2**.

A series of ketones of structures A and B incorporating different groups L were synthesized. On the basis of a combination of criteria, viz., (i) stability of ketone A and (ii) subsequent facile elimination of L from B to generate **2**, the imidazole moiety was selected as the group L of choice. Interestingly, compounds containing nonheteroaromatic N-linked groups, such as the morpholino ketone **3**, preferred to undergo the retro-Mannich reaction rather than the desired retro-Michael (see Scheme II). Such a sequence resulted in the liberation of the desyl chloride **4** rather than the α,β-unsaturated ketone **2**.

Thus the α-chloro ketone **5** was selected as the target compound. The α-bromo ketone **6** and α-fluoro ketone **7** were prepared for comparison purposes. It was predicted that, on the basis of literature values for the reduction

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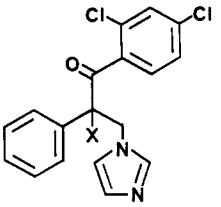
Table II. In Vitro Activity of Test Compounds against a Range of Aerobic Bacteria[a]

organism	MIC, μg/mL						
	5	6	7	2	9	11	polymyxin
Staphylococcus aureus ATCC 25923	25	1.5	50	<0.8	<0.8	25	25
Streptococcus pyrogenes ATCC 19615	1.5	<0.8	6.2	<0.8	<0.8	6.2	1.5
Pseudomonas aeruginosa ATCC 27853	>100	>100	>100	>100	>100	>100	3.1
Proteus vulgaris ATCC 13315	>100	12.5	>100	6.2	6.2	>100	1.5
Klebsiella pneumoniae ATCC 13883	>100	>100	>100	>100	>100	>100	<0.8
Escherichia coli ATCC 25922	>100	>100	>100	>100	>100	>100	<0.8

[a] For methodology see Experimental Section.

potential of phenacyl bromides and phenacyl fluorides (see Table III), 6 and 7 would have inappropriate reduction potentials to demonstrate the desired selectivity of action.



X

(5) Cl
(6) Br
(7) F

Chemistry

The target α-chloro ketone 5 and the related α-bromo ketone 6 were prepared as outlined in Scheme III. The allylic alcohol 8 was prepared by treatment of 2,4-dichlorobenzaldehyde with the Grignard reagent derived from α-bromostyrene. Oxidation of this allylic alcohol with barium manganate in refluxing toluene afforded the α,β-unsaturated ketone 2 in high yield. This α,β-unsaturated ketone was found to be prone to polymerization and could only be satisfactorily analyzed by NMR. Michael addition of imidazole to the α,β-unsaturated ketone 2 afforded the ketone 9. The lithium enolate of this ketone, generated with lithium hexamethyldisilazide in tetrahydrofuran, was treated with *N*-chlorosuccinimide in hexamethylphosphoramide to afford the desired α-chloro ketone 5 in good yield. Treatment of the same enolate with bromine afforded the corresponding α-bromo ketone 6.

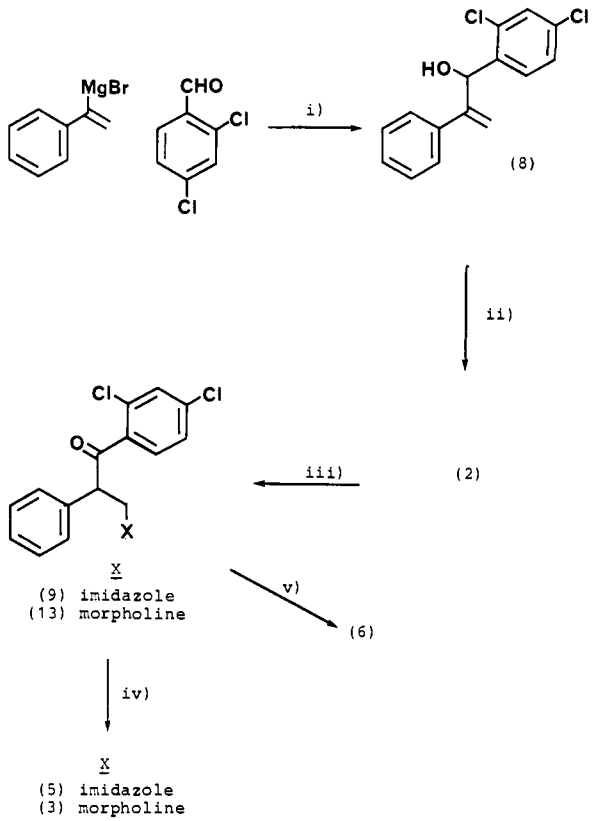
Compound 3, the morpholino ketone analogue of 5, was prepared by the same route. The compound was stable when isolated as the hydrochloride salt but on chromatography on silica gel the compound underwent a retro-Mannich reaction to leave the desyl chloride 4 as the only isolable product.

The α-fluoro ketone 7, was prepared as outlined in Scheme IV. The α,β-unsaturated ketone 2 was epoxidized with 30% hydrogen peroxide in methanolic sodium hydroxide to yield the epoxy ketone 10. Treatment of this epoxy ketone with imidazole afforded the α-hydroxy ketone 11 in very high yield. This hydroxy ketone was treated with (diethylamido)sulphur trifluoride (DAST) to yield the desired α-fluoro ketone. A similar synthesis of a series of α-hydroxy ketones analogous to 11 and their activity as antifungal agents has recently been reported by Ogata et al.[17]

Results and Discussion

The in vitro activities against a range of anaerobic bacteria for the three α-halo ketones, 5, 6, and 7, the ketone

Scheme III[a]



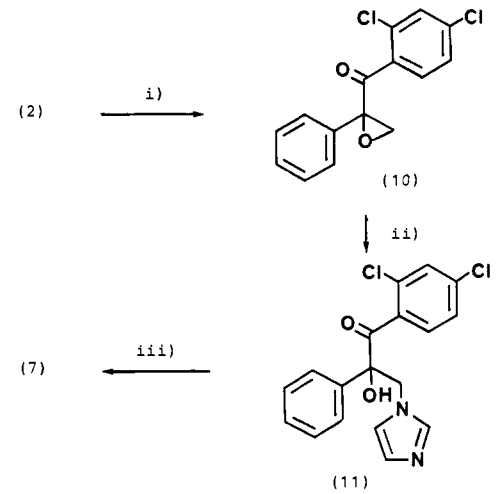
[a] (i) THF. (ii) $BaMnO_4$, toluene, Δ, 12 h. (iii) Imidazole, EtOH, room temperature, overnight. (iv) (a) Lithium hexamethyldisilazide, THF, −78 °C; (b) *N*-chlorosuccinimide, HMPA → room temperature. (v) (a) Lithium hexamethyldisilazide, THF, −78 °C; (b) Bromine, pentane → room temperature overnight.

9, the α,β-unsaturated ketone 2, and the α-hydroxy ketone intermediate 11 are shown in Table I. The in vitro activities of the same compounds against selected aerobes are presented in Table II.

The α-chloro ketone 5 is clearly comparable in potency with the intended product of its reduction 9, subsequent disproportionation 2, and metronidazole against anaerobic bacteria. In addition 5, 9, and 2, retain activity against metronidazole-resistant strains of *Bacteroides fragilis* and, unlike metronidazole, are active against *Propionibacterium acnes*.

The α-bromo ketone 6 would also appear to share the activity of metronidazole; however, careful inspection of the stability of 6 by HPLC under in vitro test conditions, but lacking the test organism, reveal that it is rapidly converted to the reduction product 9 and that this rapidly

Scheme IV[a]



[a] (i) H_2O_2, NaOH (MeOH). (ii) Imidazole, *i*-PrOH. (iii) SF_3NEt_2, CCl_4/CH_2Cl_2, −70 °C → 0 °C.

Table III. Half-Wave Reduction Potentials of Phenacyl Halides[a,b]

compd	$E_{1/2}$, mV
phenacyl bromide	−160
phenacyl chloride	−540
phenacyl fluoride	−1020

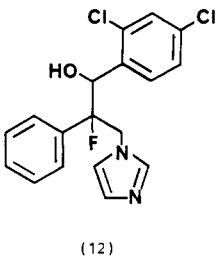
[a] The above literature data[18] was measured by using a standard calomel electrode and 10% EtOH/McIlvaine buffer (pH 7.1). [b] The $E_{1/2}$ of metronidazole under similar conditions was measured[19] to be −581 mV. Unfortunately under these conditions the compounds **5** and **6** failed to provide meaningful data.

disappears from the media. This contrasts with the α-chloro ketone **5** which is completely stable under these conditions. We suggest that the α-bromo ketone is so easily reduced by constituents in the in vitro test media, such as cysteine and other thiols, that it undergoes facile conversion to the ketone **9** and then subsequent breakdown to the α,β-unsaturated ketone **2**. Thus the overall transformation of **6** into **2** might proceed in an indiscriminant fashion which does not require the involvement of the bacterial electron transport chain.

Unfortunately we were not able to identify HPLC conditions suitable for detecting **2** as the final breakdown product to confirm this hypothesis. However, we can demonstrate by NMR monitoring that chemical reaction of **6** (but not **5**) with soft nucleophiles such as thiophenol gives a quantitative conversion to the ketone **9** via reduction but with no evidence of any other products.

These findings can be correlated with the predicted values of the reduction potentials of the α-bromo and α-chloro ketones as extrapolated from the phenacyl halide series (Table III).[18] When compared to metronidazole measured under the same conditions,[19] it is clear that the α-bromo ketone should be far more easily reduced. In contrast, the α-fluoro ketone **7** (which may generate the fluorohydrin **12** rather than or as well as ketone **9**[18,20]) requires a substantially greater reduction capability than is necessary for metronidazole.

On this basis it is not therefore surprising that this compound **7** is much less active. On the basis of these



(12)

predictions the α-chloro ketone **5** is clearly optimal for our purposes and has the ability to be an effective and specific agent against anaerobic bacteria. Unlike metronidazole, this compound was nonmutagenic in the Ames mutagenicity assay.

The above findings can no more than suggest that the activity of **5** against anaerobic bacteria might be due to the intended mode of action that prompted its synthesis. It is possible that the compounds **5** and **9** have antianaerobic activity without need of conversion to **2**.

However, given (a) the inactivity of **11** and, in particular, **7** against anaerobic bacteria and (b) the retention of high activity of **9** and **2** against aerobic bacteria such as *Staphylococcus aureus* and *Streptococcus pyrogenes* while the activity of **5** against such species is greatly reduced, it is the opinion of the authors that the activity of **5** is due to its reduction within the anaerobic organism. It is accepted that this cannot be considered proven. If the activity of **5** is indeed due to its bioreduction, and that this bioreduction is carried out by the same bacterial ferredoxin or other election-transfer protein that is responsible for the bioreduction of metronidazole, then the apparent lack of specificity beyond reduction potential exhibited by such a protein is perhaps remarkable. This would suggest that a wide range of molecular structures might be devised which would share specificity for organisms possessing such electron-transfer proteins.

Experimental Section

Melting points were determined with a Reichert Thermovar melting point apparatus and are uncorrected. Novel compounds were routinely analyzed by IR (Perkin-Elmer 197) and NMR (Bruker WM-250).

1-(2,4-Dichlorophenyl)-2-phenylpropen-1-ol (8). A mixture of magnesium (0.73 g, 30 mM) and α-bromostyrene (4.7 g, 26 mM) in dry THF (75 mL) was heated to reflux until the magnesium had dissolved and then treated with a solution of 2,4-dichlorobenzaldehyde (4.7 g, 26 mM) and THF (25 mL). The reaction was maintained at reflux for 4 h before being cooled and poured into dilute HCl. The resulting mixture was extracted with ethyl acetate, the organic phase was washed with water and dried over anhydrous magnesium sulfate, and the solvent was removed in vacuo to leave a gum, which was chromatographed on silica gel with ethyl acetate/hexane as eluent (1:1) to afford, as an oil, the alcohol **8**: yield 5 g (67%); NMR ($CHCl_3$-*d*) δ 3.2–3.4 (1 H, b, exchangeable with D_2O), 5.3 (1 H, s), 5.5 (1 H, s), 6.1 (1 H, s), and 7.2–7.6 (8 H, m). Anal. ($C_{15}H_{12}Cl_2O$) C, H.

1-(2,4-Dichlorophenyl)-2-phenylpropen-1-one (2). To a solution of the alcohol **8** (4 g, 14.3 mM) in toluene (100 mL) was added barium manganate (5 g, 19.5 mM) and the resulting mixture heated at reflux under an atmosphere of nitrogen for 12 h. The mixture was cooled and filtered and the solvent removed in vacuo to afford as a gum, the α,β-unsaturated ketone **2**: yield 4.3 g (86%); NMR ($CHCl_3$-*d*) δ 5.75 (1 H, s), 6.30 (1 H, s), and 7.25–7.60 (8 H, m).

1-(2,4-Dichlorophenyl)-3-(1*H*-imidazol-1-yl)-2-phenylpropan-1-one (9). A solution of the ketone **2** (16 g, 57.7 mM) in ethanol (150 mL) was treated with imidazole (11.2 g, 164.5 mM) and stirred overnight at room temperature. The solvent was removed in vacuo and the resulting gum dissolved in dichloromethane. The solution was washed with water and dried over anhydrous magnesium sulfate and the solvent removed in vacuo to leave a gum. This gum chromatographed on silica gel with

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methanol/dichloromethane (1:19) as eluent to give material that when treated with ethereal HCl afforded the hydrochloride salt of **9**: yield 8.9 g (41%); mp 110 °C; NMR ($(CH_3)_2SO$-d_6) δ 4.8–5.0 (2 H, m), 5.4–5.6 (1 H, t), 7.8–8.0 (10 H, m), and 9.1 (1 H, s). Anal. ($C_{18}H_{15}Cl_3N_2O{\cdot}0.5H_2O$) C, H, N.

1-(2,4-Dichlorophenyl)-3-(1*H*-morpholin-1-yl)-2-phenylpropan-1-one (3). This compound was prepared by the same procedure as for **9** but before chromatography the material solidified. Recrystallization from ethyl acetate/hexane afforded, as a white solid, the desired ketone **3**: yield 17%; mp 76–81 °C; NMR ($CHCl_3$-d) δ 2.4–2.5 (4 H, m), 2.6–2.7 (1 H, dd), 3.3–3.4 (1 H, dd), 3.6–3.7 (4 H, m), 4.6–4.7 (1 H, dd), and 7.2–7.4 (8 H, m). Anal. ($C_{19}H_{19}C_{12}NO_2$) C, H, N.

2-Chloro-1-(2,4-dichlorophenyl)-3-(1*H*-imidazol-1-yl)-2-phenylpropan-1-one (5). To a stirred solution of lithium hexamethyldisilazide (5.5 mL, 1 M in THF) in dry THF (20 mL) at −78 °C under an atmosphere of nitrogen was added dropwise a solution of the free base of the ketone **9** (1.7 g, 4.5 mM), in dry THF (5 mL). The mixture was stirred for 30 min and then a solution of *N*-chlorosuccinimide (810 mg, 6.1 mM) in dry HMPA (8 mL) added. The mixture was allowed to warm to room temperature and saturated aqueous ammonium chloride added. The organic phase was removed and the aqueous phase extracted with ethyl acetate. The combined organic extracts were washed with brine and dried over anhydrous magnesium sulfate, and the solvent was removed in vacuo to leave an oil which was chromatographed on silica gel with methanol/dichloromethane (1:99) as eluent to give material which on treatment with ethereal HCl afforded as a very hydroscopic solid, the hydrochoride salt of the α-chloro ketone **5**: yield 1.5 g (73%); NMR ($(CH_3)_2SO$-d_6) δ 5.40 (2 H, dd, *J* 14 and 19 Hz), 6.54 (1 H, d, *J* 8 Hz), 7.28–7.40 (2 H, m), 7.59 (6 H, bs), 7.81 (1 H, d, *J* 2 Hz), and 8.97 (1 H, bs). Anal. ($C_{18}H_{14}Cl_4N_2O{\cdot}0.5H_2O$) C, H, N.

2-Chloro-1-(2,4-dichlorophenyl)-3-(1*H*-morpholin-1-yl)-2-phenylpropan-1-one (3). This compound was prepared by the method used for compound **5** but before chromatography the crude material was treated with ethereal HCl. The resulting solid was crystallized from ethanol as the hydrochloride salt of **3**: yield 17%; mp 119–122 °C; NMR ($(CH_3)_2SO$-d_6 + D_2O) δ 2.8–2.9 (4 H, m), 3.2–3.3 (1 H, d), 3.4–3.5 (1 H, d), 3.6–3.7 (4 H, m), 6.9 (1 H, d), 7.1 (1 H, d), 7.4–7.5 (4 H, m), and 7.6–7.7 (2 H, m). Anal. ($C_{19}H_{19}Cl_4NO_2$) C, H, N.

2-Bromo-1-(2,4-dichlorophenyl)-3-(1*H*-imidazol-1-yl)-2-phenylpropan-1-one (6). To a stirred solution of lithium hexamethyldisilazide (3.3 mL, 1 M in THF) in dry THF (15 mL) at −78 °C under an atmosphere of nitrogen was added dropwise a solution of the free base of the ketone **9** (1.0 g, 2.6 mM), in dry THF (5 mL). The remaining mixture was stirred for 40 min and then a solution of bromine (0.5 g, 3.1 mM) in pentane (5 mL) added. The mixture was allowed to warm to room temperature overnight and then saturated aqueous ammonium chloride added. The organic phase was separated and the aqueous phase extracted with ethyl acetate. The combined organic extracts were washed with brine and dried over anhydrous magnesium sulfate, and the solvent was removed in vacuo to leave an oil which was chromatographed on silica gel with methanol/dichloromethane (3:97) as eluent. This gave material which upon treatment with ethereal HCl afforded the hydrochloride salt of the α-bromo ketone **6**: yield 800 mg (60%); mp 108–113 °C; NMR ($(CH_3)_2SO$-d_6) δ 5.41 (2 H, dd, *J* 14 and 19 Hz), 6.67 (1 H, d, *J* 8 Hz), 7.15 (1 H, s), 7.30 (1 H, dd, *J* 2 and 8 Hz), 7.56 (6 H, s), 7.81 (1 H, d, *J* 2 Hz), and 8.93 (1 H, s). Anal. ($C_{18}H_{14}BrCl_3N_2O{\cdot}0.5H_2O$) C, H, N.

1-(2,4-Dichlorophenyl)-2,3-epoxy-2-phenylpropan-1-one (10). A solution of the α,β-unsaturated ketone **2** (720 mg, 2.6 mM) in methanol (100 mL) was cooled in an ice bath and treated with aqueous sodium hydroxide (1.5 mL, 2 M) and 30% hydrogen peroxide (5 mL). The mixture was stirred at room temperature for 30 min and then quenched with saturated aqueous ammonium chloride. The solution was concentrated to half its original value in vacuo and then extracted with diethyl ether. The organic phase was dried over anhydrous magnesium sulfate and the solvent removed in vacuo to leave a gum which was chromatographed on silica gel with ethyl acetate/hexane (1:19) as eluent to afford as an oil the epoxy ketone **10**: yield 500 mg (66%); NMR ($CHCl_3$-d) δ 3.12 (1 H, d, *J* 6 Hz), 3.24 (1 H, d, *J* 6 Hz), 6.92 (1 H, dd, *J* 2 and 8 Hz), 7.07 (1 H, m), 7.30 (1 H, m), 7.40 (3 H, m), 7.56 (1 H, m), and 7.67 (1 H, d, *J* 8 Hz). Anal. ($C_{15}H_{10}Cl_2O_2$) C, H.

1-(2,4-Dichlorophenyl)-2-hydroxy-3-(1*H*-imidazol-1-yl)-2-phenylpropan-1-one (11). To a solution of the epoxy ketone **10** (50 mg, 0.17 mM) in 2-propanol (3 mL) was added imidazole (100 mg, 1.5 mM), and the mixture was heated at 100 °C for 30 min. The solvent was removed, the residue redissolved in dichloromethane, and washed with water. The organic phase was dried over anhydrous magnesium sulfate and the solvent removed in vacuo to afford as a white solid, the α-hydroxy ketone **11**: yield 48 mg (90%); mp 175–177 °C; NMR ($CHCl_3$-d) δ 2.10 (1 H, vbs), 4.17 (1 H, d, *J* 15 Hz), 4.87 (1 H, d, *J* 15 Hz), 6.60 (1 H, s), 6.72 (1 H, s), 6.93 (1 H, d, *J* 8 Hz), 7.02 (1 H, dd, *J* 2 and 8 Hz), 7.35 (2 H, m), 7.40 (3 H, m), and 7.62 (2 H, m). Anal. ($C_{18}H_{14}Cl_2N_2O_2$) C, H, N.

1-(2,4-Dichlorophenyl)-2-fluoro-3-(1*H*-imidazol-1-yl)-2-phenylpropan-1-one (7). To a solution of the α-hydroxy ketone **11** (500 mg, 1.4 mM) in carbon tetrachloride/dichloromethane (100 mL, 1:1) at −70 °C under an atmosphere of nitrogen was added (diethylamido)sulfur trifluoride (1.5 mL, 11.4 mM), and the solution was allowed to warm to 0 °C. After 15 min water was added and the organic phase was further washed with water and dried over anhydrous magnesium sulfate, and the solvents were removed in vacuo. The residue was chromatographed on silica gel with methanol/dichoromethane (1:19) as eluent to afford a gum which on treatment with ethereal HCl gave the hydrochloride salt of **7**: yield 125 mg (25%); mp 155–158 °C; NMR ($(CH_3)_2SO$-d_6) δ 4.45 (H, dd, *J* 14 and 18 Hz), 4.90 (1 H, dd, *J* 2.5 and 14 Hz), 6.65 (1 H, d, *J* 8 Hz), 6.90 (1 H, bs), 7.00 (1 H, bs), 7.10 (1 H, dd, *J* 2 and 8 Hz), 7.45 (6 H, m) and 7.6 (1 H, bs). Anal. ($C_{18}H_{14}Cl_3FN_2O{\cdot}0.5H_2O$) C, H, N.

Biological Methods. Determination of Minimum Inhibitory Concentrations. Minimum inhibitory concentrations (MIC's) were determined by broth dilution in 96-well microtitre plates (Dynatech). Aliquots of drug, medium, and inoculum were added to the wells by using an eight-channel pipet (Titertek). Drugs were dissolved in 20% polyethylene glycol 200/water to give a stock solution containing 200 μg/mL. Serial 2-fold dilutions of this stock were made in the wells of the microtitre plate. Final test concentrations ranged from 0.8–100 μg/mL. The final inoculum concentration was 10^5 organisms/mL. MIC's were read after 48 h incubation in a Forma Anaerobic Chamber (anaerobes) or in a conventional incubator (aerobes) at 37 °C. The MIC was taken as the lowest concentration at which there was no visible growth.

HPLC Studies. These were carried out by using a Gilson HPLC system equipped with an Ultrasphere-ODS 5-μm column. Samples were run under reverse phase in 75% methanol/25% 0.1 M phosphate buffer with the detector set at 254 nm. The flow rate was 1 mL/min. Compounds were dissolved initially in methanol and this stock diluted with methanol or broth to give a final concentration of 100 μM. Samples (50 μM) were applied to the column for each run.

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Registry No. **2**, 106849-63-2; **3**·HCl, 134529-51-4; **4**, 134529-52-5; **5**·HCl, 107316-26-7; **6**·HCl, 134529-53-6; **7**·HCl, 134529-54-7; **8**, 106849-64-3; **9**, 106849-65-4; **10**, 111299-49-1; 11, 134529-55-8; **13**, 134529-56-9; α-bromostyrene, 98-81-7; imidazole, 288-32-4; morpholine, 110-91-8; 2,4-dichlorobenzaldehyde, 874-42-0.