Nucleophilic Addition of 2-, 3-, or 4-[2-(Methylamino)ethyl]pyridine to the Aziridine, 7-Methyl-7-azabicyclo[4.1.0]heptane

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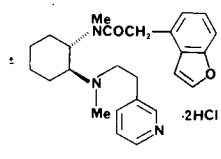
Received February 22, 1989

The synthesis of *trans*-(±)-*N*-methyl-*N*-[2-[methyl[2-(3-pyridyl)ethyl]amino]cyclohexyl]-4-benzofuranacetamide dihydrochloride, **1** which is a 3-[2-(methylamino)ethyl]pyridyl derivative of the kappa opioid analgesic *trans*-(±)-*N*-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]benzofuran-4-acetamide monohydrochloride, **2** is described. The key intermediate is *trans*-(±)-*N*,*N*'-dimethyl-*N*-[2-(3-pyridyl)ethyl]-1,2-cyclohexanediamine, **9** which is formed by nucleophilic addition of 3-[2-(methylamino)ethyl]pyridine **6** to the aziridine, 7-methyl-7-azabicyclo[4.1.0]heptane, **4**. During attempts to prepare the 2- or 4-isomeric pyridyl derivatives of **1** it was discovered that both 2- or 4-[2-(methylamino)ethyl]pyridine, **5** or **7** are converted to *N*-methyl-*N*,*N*-di-[2-(2-pyridyl)ethylamine] **11** and *N*-methyl-*N*,*N*-di[2-(4-pyridyl)ethylamine] **13** respectively by refluxing in toluene in the presence of ammonium chloride. The 3-isomer, **6** is unchanged after treatment under identical conditions. Careful control of the reaction conditions enabled the aziridine **4** to be ring opened with the pyridyl amines **5** or **7** to give the 1,2-diamines *trans*-(±)-*N*,*N*'-dimethyl-*N*-[2-(2-pyridyl)ethyl]-1,2-cyclohexanediamine, **8** or *trans*-(±)-*N*,*N*'-dimethyl-*N*-[2-(4-pyridyl)ethyl]-1,2-cyclohexane diamine **10** respectively.

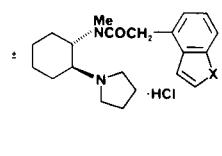
J. Heterocyclic Chem., **27**, 147 (1990).

As part of an ongoing research programme aimed at discovering selective kappa opioid analgesic drugs [1,2,3,4] it was required to synthesize *trans*-(±)-*N*-methyl-*N*-[2-[methyl[2-(3-pyridyl)ethyl]amino]cyclohexyl]-4-benzofuranacetamide dihydrochloride, **1** which is a 3-[2-(methylamino)ethyl]pyridyl derivative of the highly kappa selective opioid analgesics *trans*-(±)-*N*-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]benzofuran-4-acetamide monohydrochloride, **2** and *trans*-(±)-*N*-methyl-*N*-[2-(1-pyrrolidinyl)-cyclohexyl]benzo[*b*]thiophene-4-acetamide monohydrochloride, **3** (PD 117302) [3,5]. The 2-, 3- or 4-[2-(methylamino)ethyl]pyridyl group was of interest because the incorporation of an *N*-phenylethylamino group into the analgesic drugs morphine, fentanyl, pethidine and the phenylpiperidines has been reported to increase analgesic potency [6,7] but the effect of the *N*-pyridylethylamino group has not been fully studied.

The synthetic route planned to provide derivatives of the target molecule **1** involved nucleophilic ring opening of 7-methyl-7-azabicyclo[4.1.0]heptane, **4** with 2-, 3- or 4-[(2-methylamino)ethyl]pyridine **5**, **6**, **7** followed by acylation of the resulting *trans*-(±)-*N*,*N*'-dimethyl-*N*-[2-(2-pyridyl)-ethyl]-1,2-cyclohexanediamine **8**, *trans*-(±)-*N*,*N*'-dimethyl-*N*-[2-(3-pyridyl)ethyl]-1,2-cyclohexanediamine **9** or *trans*-(±)-*N*,*N*'-dimethyl-*N*-[2-(4-pyridyl)ethyl]-1,2-cyclohexane diamine **10** with 4-benzofuranacetic acid and 1,1'-carbonyl-bis-1*H*-imidazole (Scheme 1). However, when the amine **5** was treated with the aziridine **4** and a catalytic amount of ammonium chloride using the usual conditions for *trans*-1,2-cyclohexanediamine formation [3,4] the major product isolated after distillation was found to be *N*-methyl-*N*,*N*-di-[2-(2-pyridyl)ethylamine] **11**. To investigate this further **5** alone was treated in refluxing toluene with a catalytic amount of ammonium chloride for



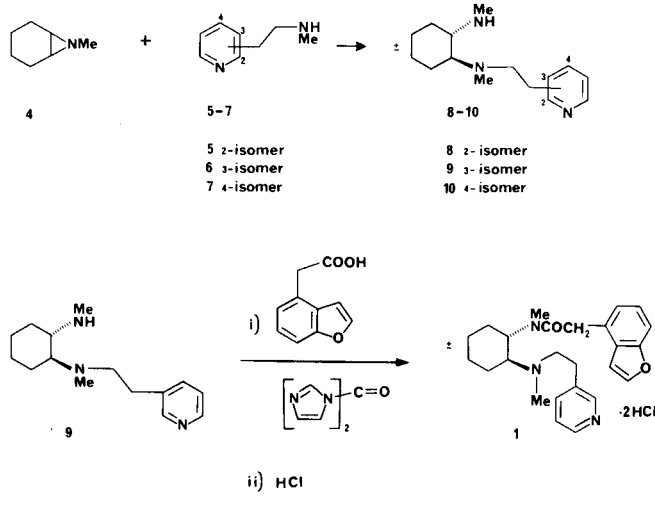
1



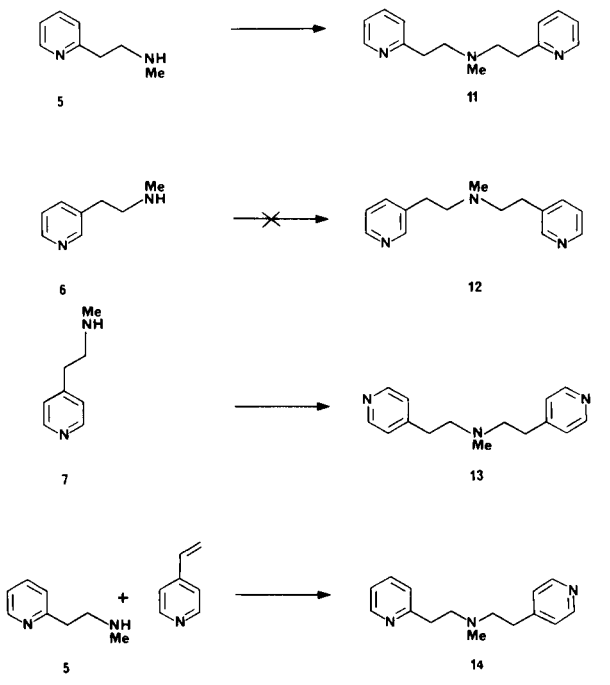
2 X=O
3 X=S (PD 117302)

28 hours. Less than 5% of **5** remained and the major product was **11** (69%) (Scheme 2). The same product was formed when compound **5** was treated with ammonium chloride at 100-120° without solvent; but compound **5** was recovered unchanged after treatment with a catalytic amount of potassium carbonate. Therefore an acid catalysed mechanism is proposed which invokes the formation of 2-vinylpyridine followed by Michael addition of the starting amine (Scheme 3). When the 4-isomer **7** was treated

Scheme 1

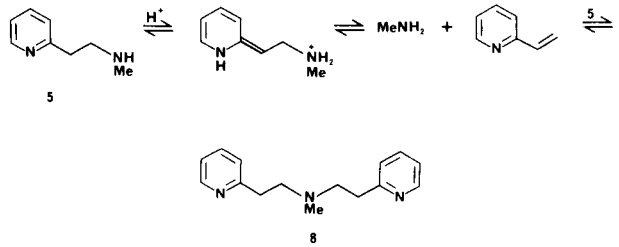


Scheme 2



under identical conditons of acid catalysis it decomposed at a rate similar to that of the 2-isomer **5**, the major product being *N*-methyl-*N*,*N*-di-[2-(4-pyridyl)ethylamine] **13** (71%). It is proposed that this proceeds via the formation of 4-vinylpyridine by a mechanism similar to that outlined in Scheme 3.

Scheme 3



If this mechanism is correct then the formation of 3-vinylpyridine from the 3-substituted isomer **6** should be much less facile than the formation of 2- or 4-vinylpyridine from the isomers **5** or **7**. To test this hypothesis compound **6**, prepared from methyl 3-pyridylacetate and methylamine followed by borane in tetrahydrofuran, was treated with ammonium chloride and toluene under identical conditions to the 2- and 4-isomers. Compound **6** was isolated unchanged in 90% yield and none of the corresponding condensation product *N*-methyl-*N*,*N*-di-[2-(3-pyridyl)ethylamine] **12** was detected. To investigate whether 2- and 4-vinylpyridines are actually reactive intermediates during the formation of compounds **11** and **13**, 4-vinylpyridine was treated with amine **5** under similar conditions to those used to effect formation of the condensation product **11**. The major product was *N*-methyl-*N*-[2-(4-pyridyl)ethyl]-(2-pyridyl)ethylamine **14** (74% yield) arising from Michael addition of amine **5** to 4-vinylpyridine. None of the symmetrical amine **11** was detected during this reaction and no 4-vinylpyridine was detected by tlc during the conversion of **7** into **13**. These observations indicate that the vinylpyridine is indeed an intermediate in the formation of amines **11** and **13** and that under these acidic conditions the nucleophilic addition to 4-vinylpyridine is faster than the elimination of methylamine. The addition of both carbon and nitrogen nucleophiles to 2- and 4-vinylpyridines is well established and is known to be much more facile than nucleophilic addition to 3-vinylpyridine [8,9].

Having established the relative instability of **5** and **7** compared to **6** the aziridine opening reaction was reinvestigated. It was found that if the temperature was kept at 95-100° the desired diamines **8**, **9** and **10** were formed in 42%, 49% and 26% yield respectively. The diamine **9** was converted into **1** as described above.

EXPERIMENTAL

Melting points were determined using a Reichert Thermovar hot-stage apparatus and are uncorrected. Proton nmr spectra were recorded on a Bruker AM 300 spectrometer or a Jeol PMX-60SI spectrometer; chemical shifts were recorded in parts per million downfield from tetramethylsilane. The ir spectra were recorded using a Perkin-Elmer 1750 spectrophotometer. Silica gel used for chromatography was Kieselgel-60 (230-400 mesh) (E. Merck A. G., Darmstadt, Germany). Electron impact mass spectra were recorded using on a Finnegan 4500 spectrometer. Elemental analyses were determined by C.H.N. Analysis Limited, Leicester, U.K. 2-[2-(Methylamino)ethyl]pyridine, 4-[2-(methylamino)ethyl]pyridine, 4-vinylpyridine, 3-pyridylacetic acid and 1,1'-carbonyl-bis-1*H*-imidazole were obtained from Aldrich Chemical Company or from Pfaltz & Bauer, Inc.

3-[2-(Methylamino)ethyl]pyridine (**6**).

3-Pyridylacetic acid (7.78 g, 44.8 mmoles) was dissolved in methanol (60 ml) containing a trace of hydrogen chloride and heated under reflux. After 5 hours 40% aqueous methylamine (20 ml, 0.26 mole) was added and after a further 3 hours at reflux this mixture was concentrated *in vacuo*, poured into saturated aqueous potassium carbonate (100 ml) and extracted with dichloromethane (3 x 70 ml). Evaporation of the organic layers gave an oil (5.2 g); ir (liquid film): 3285 (NH), 1656 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): 60 MHz δ 2.76 (d, 3H, J = 4 Hz, CH_3), 3.50 (s, 2H, CH_2), 6.40 (br s, 1H, NH), 7.12 (m, 2H), 8.20 (m, 2H). This oil (4.8 g, 32 mmoles) was dissolved without further purification in tetrahydrofuran (50 ml), cooled in an ice-water bath and treated with borane in tetrahydrofuran (1 *M* solution, 78 ml, 78 mmoles). The solution was heated to reflux and further additions of the borane in tetrahydrofuran solution were made as follows: 20 ml after 2.5 hours, 75 ml after 6 hours. After a total of 12

hours the reaction mixture was cooled to 0° and treated with water (50 ml, dropwise) followed by hydrochloric acid (10 *M*, 75 ml). After 2 hours at 21° the mixture was concentrated *in vacuo*, basified with an excess of potassium hydroxide and extracted with dichloromethane (3 x 150 ml) to give an oil (3.9 g). Distillation gave compound **6** (1.4 g, 23%) as a colourless liquid, bp 121-122°/15 mm Hg (lit [10] 124-128°/24 mm Hg); ^{1}H nmr (deuteriochloroform); 300 MHz δ 2.48 (s, 3H, CH_3), 2.86 (m, 4H), 2.91 (s, 1H, NH), 7.22 (dd, 1H, J = 8.0, 5.0 Hz, H-5), 7.54 (ddd, 1H, J = 8.0, 0.5, 0.5 Hz, H-4), 8.47 (m, 2H, H-2, H-6); ms: 137 (M+).

N-Methyl-*N*,*N*-di-[2-(2-pyridyl)ethylamine] (**11**).

2-[2-(Methylamino)ethyl]pyridine **5** (8.0 g, 59 mmoles), toluene (20 ml) and ammonium chloride (100 mg, 1.9 mmoles) were stirred and heated to reflux for 28 hours. The mixture was poured into aqueous potassium carbonate (100 ml) and extracted with ether (2 x 100 ml). The combined organic fractions were dried (potassium carbonate) and distilled to give **11** as a pale yellow liquid (4.9 g, 20 mmoles, 68%), bp 126-127°/0.08 mm Hg; ir (liquid film): 1595 (arC=C) cm^{-1}; ^{1}H nmr (deuteriochloroform): 300 MHz δ 2.55 (s, 3H, NMe), 3.10 (s, 8H, 4 x CH_2), 7.12 (dd, 2H, J = 8.0, 5.0 Hz, 2 x H-5), 7.18 (d, 2H, J = 8.0 Hz, 2 x H-3), 7.59 (ddd, 2H, J = 8.0, 8.0, 1.0 Hz, 2 x H-4), 8.49 (dd, 2H, J = 5.0, 1.0 Hz, 2 x H-6); ms: 241 (M^+ 1%), 149 (100), 106 (65).

Anal. Calcd. for $C_{15}H_{19}N_3$: C, 74.7; H, 7.9; N, 17.4. Found: C, 74.4; H, 8.1; N, 17.1.

The product, **11**, was also isolated by treating **5** (1.0 g, 7.4 mmoles) with ammonium chloride (20 mg, 0.37 mmole) without solvent at 100-120° for 18 hours in 33% yield.

N-Methyl-*N*,*N*-di-[2-(4-pyridyl)ethylamine] (**13**).

2-[4-(Methylamino)ethyl]pyridine **7** (8.0 g, 59 mmoles), toluene (20 ml) and ammonium chloride (0.10 g, 1.9 mmoles) were stirred and heated to reflux for 28 hours. The mixture was poured into aqueous potassium carbonate (100 ml) and extracted with ether (2 x 100 ml). The combined organic fractions were dried (potassium carbonate) and distilled to give **13** as a pale yellow liquid (5.0 g, 21 mmoles, 71%), bp 159-160°/0.06 mm Hg; ir (liquid film): 1604 (arC=C) cm^{-1}; ^{1}H nmr (deuteriochloroform): 300 MHz δ 2.36 (s, 3H, NMe), 2.71 (m, 8H, 4 x CH_2), 7.09 (d, 4H, J = 6.0 Hz, 2 x H-2 and 2 x H-6), 8.47 (d, 4H, J = 6.0 Hz, 2 x H-3 and 2 x H-5); ms: 241 (M^+, 2), 240 (8), 149 (100).

Anal. Calcd. for $C_{15}H_{19}N_3$: C, 74.4; H, 7.9; N, 17.4. Found: C, 74.5; H, 7.9; N, 17.2.

N-Methyl-*N*-[2-(4-pyridyl)ethyl]-(2-pyridyl)ethylamine (**14**).

2-[2-(Methylamino)ethyl]pyridine **5** (0.05 g, 3.7 mmoles), toluene (2.5 ml), 4-vinylpyridine (0.39 g, 3.7 mmoles) and ammonium chloride (10 mg, 0.19 mmoles) were stirred and heated in an oil bath at 85-86° for 60 hours. Medium pressure chromatography of the resulting mixture on silica gel with dichloromethane-methanol (6:1) as eluant yielded **14** (0.66 g, 2.7 mmoles, 74%), bp 150-152°/0.06 mm Hg; ir (liquid film): 1602 (arC=C) cm^{-1}; ^{1}H nmr (deuteriochloroform): 300 MHz δ 2.38 (s, 3H, NMe), 2.70 (m, 4H, 2 x CH_2), 2.85 (m, 2H, CH_2), 2.95 (m, 2H, CH_2), 7.10 (m, 4H, H-3 and H-5 of 4-pyridyl, H-3 and H-5 of 2-pyridyl), 7.56 (ddd, 1H, J = 8.0, 8.0, 1.0 Hz, H-4 of 2-pyridyl), 8.44 (d, 2H, J = 6.0, H-2 and H-6 of 4-pyridyl), 8.51 (dd, 1H, J = 5.0, 1.0 Hz, H-2 of 2-pyridyl); ms: 241 (M^+, 1), 149 (100).

Anal. Calcd. for $C_{15}H_{19}N_3$: C, 74.7; H, 7.9; N, 17.4. Found: C, 74.6; H, 8.0; N, 17.2.

Treatment of 3-[2-(methylamino)ethyl]pyridine **6** with Ammonium Chloride.

3-[2-(Methylamino)ethyl]pyridine **6** (0.20 g, 1.5 mmoles), toluene (1 ml) and ammonium chloride (5 mg, 0.09 mmole) were stirred and heated to reflux for 72 hours. Medium pressure chromatography of the resulting mixture on silica gel with dichloromethane-methanol-dimethylamine (92:7:1) eluant yielded unchanged **6** (0.18 g, 90%). No other products were isolated and no components with R_f values similar to those observed for compounds **11** and **13** were detected by tlc.

Typical Procedure for Formation of Diamines **8**, **9**, **10**.

trans-(±)-*N*,*N*'-Dimethyl-*N*-[2-(2-pyridyl)ethyl]-1,2-cyclohexanediamine (**8**).

2-[2-(Methylamino)ethyl]pyridine **5** (0.50 g, 3.7 mmoles) and 7-methyl-7-azabicyclo[4.1.0]heptane **4** [11] (0.40 g, 3.6 mmoles) were dissolved in water (0.5 ml) containing ammonium chloride (20 mg, 0.37 mmole) and heated in an oil bath at 95-100° for 14 hours. The resulting mixture was poured into 1.0 *M*-aqueous potassium hydroxide solution (100 ml) and extracted with ether (3 x 20 ml). The combined organic layers were dried (potassium carbonate), concentrated *in vacuo* and purified by medium pressure chromatography on silica gel with ethyl acetate-methanol-dimethylamine (97:2:1) as eluant to give **8** (0.41 g, 1.7 mmoles, 42%); ^{1}H nmr (deuteriochloroform): 300 MHz δ 0.9 (m, 1H), 1.2 (m, 3H), 1.8 (m, 3H), 2.1 (m, 4H), 2.15 (s, 3H, NMe), 2.27 (s, 3H, NMe), 3.0-2.6 (m, 4H, NCH_2CH_2), 7.08 (dd, 1H, J = 8.0, 5.0 Hz, H-3), 7.15 (d, 1H, J = 8.0 Hz, H-5), 7.57 (ddd, 1H, J = 8.0, 8.0, 1.5 Hz, H-4), 8.53 (dd, 1H, J = 5.0, 1.5 Hz, H-2); ir (liquid film): 3401 (NH), 1594 (arC=C) cm^{-1}; ms: 247 (M^+, 2), 175 (15), 155 (100).

Anal. Calcd. for $C_{15}H_{25}N_3$: C, 72.83; H, 10.19; N, 16.99. Found: C, 72.48; H, 10.29; N, 16.81.

trans-(±)-*N*,*N*'-Dimethyl-*N*-[2-(3-pyridyl)ethyl]-1,2-cyclohexanediamine (**9**).

Prepared by the above procedure using **6** (0.50 g, 3.7 mmoles) to give **9** (0.45 g, 1.8 mmoles, 49%); ^{1}H nmr (deuteriochloroform): 300 MHz δ 0.85 (m, 1H), 1.1 (m, 3H), 1.8 (m, 3H), 2.2 (m, 4H), 2.10 (s, 3H, NMe), 2.25 (s, 3H, NMe), 2.7-2.4 (m, 4H, NCH_2CH_2), 7.15 (dd, 1H, J = 8.0, 5.0 Hz, H-3), 7.45 (d, 1H, J = 8.0 Hz, H-4), 8.38 (br s, 2H, H-2 and H-6); ir (liquid film): 3400 (NH), 1600 (arC=C) cm^{-1}; ms: 247 (M^+, 1), 175 (5), 155 (100).

Anal. Calcd. for $C_{15}H_{25}N_3$: C, 72.83; H, 10.19; N, 16.99. Found: C, 72.45; H, 10.01; N, 16.70.

trans-(±)-*N*,*N*'-Dimethyl-*N*-[2-(4-pyridyl)ethyl]-1,2-cyclohexanediamine (**10**).

Prepared by the above procedure using **7** (0.50 g, 3.7 mmoles) to give **10** (0.24 g, 0.98 mmoles, 26%); ^{1}H nmr (deuteriochloroform): 300 MHz δ 0.9 (m, 1H), 1.12 (m, 3H), 1.8 (m, 3H), 2.1 (m, 4H), 2.14 (s, 3H, NMe), 2.26 (s, 3H, NMe), 2.7-2.5 (m, 4H, NCH_2CH_2), 7.11 (dd, 2H, J = 4.5, 1.5 Hz, H-3 and H-5), 8.48 (dd, 2H, J = 4.5, 1.5 Hz, H-2 and H-6); ir (liquid film): 3400 (NH), 1606 (arC=C) cm^{-1}; ms: 247 (M^+, 12), 175 (18), 155 (100).

Anal. Calcd. for $C_{15}H_{25}N_3$: C, 72.83; H, 10.19; N, 16.99. Found: C, 72.53; H, 9.87; N, 17.03.

trans-(±)-*N*-Methyl-*N*-[2-[methyl[2-(3-pyridyl)ethyl]amino]cyclohexyl]-4-benzofuranacetamide Dihydrochloride (**1**).

4-Benzofuranacetic acid [3] (0.21 g, 1.2 mmoles) was dissolved in tetrahydrofuran (3 ml) and treated with 1,1'-carbonylbis-1*H*-imidazole (0.21 g, 1.3 mmoles) at room temperature for 10 minutes. This solution was cooled to 0° and added to a solution of the diamine **9** (286 mg, 1.15 mmoles) in tetrahydrofuran (3 ml). After 30 minutes at room temperature the mixture was poured into aqueous potassium carbonate (300 ml) and extracted with dichloromethane (3 x 30 ml). The combined organic layers were concentrated *in vacuo*, purified by medium pressure chromatography on silica gel using dichloromethane-methanol (20:1) as eluant. The resulting product was dissolved in ether (10 ml) and treated with a slight excess of a solution of hydrogen chloride in ether. The product **1** was isolated by filtration to yield 0.33 g (0.69 mmoles, 60%), mp 142-143°; ^{1}H nmr (deuteriochloroform): 300 MHz δ 1.2-4.5 (m, 14H), 3.09 (s, 3H, NMe), 3.15 (s, 3H, NMe), 4.00 (d, 1H, J = 15 Hz, one of CH_2-benzofuran), 4.65 (d, 1H, J = 15 Hz, one of CH_2-benzofuran), 7.05-7.8 (m, 7H), 8.35 (m, 2H, H-2 and H-6 of 3-pyridyl), 8.95 (s, 1H, N^+H); 11.1 (br s, 1H, N^+H); ir (film): 3400 (NH), 1655 (CO) cm^{-1}; ms: 406 (M^+, 10), 313 (100).

Anal. Calcd. for $C_{25}H_{31}N_3O_2 \cdot 2$ HCl: C, 62.76; H, 6.95; N, 8.78. Found: C, 62.67; H, 7.17; N, 8.45.

Acknowledgement.

I warmly thank Dr. D. C. Horwell for helpful discussions throughout this work.

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