Stereospecific Reduction of 1,4,5,6-Tetrahydrobenzo[*f*]quinolin-3(2*H*)-ones with Triethylsilane–Trifluoroacetic Acid[1]

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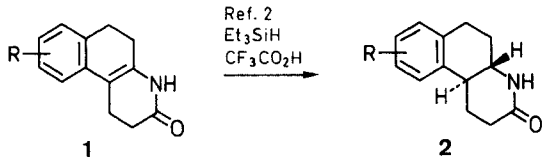
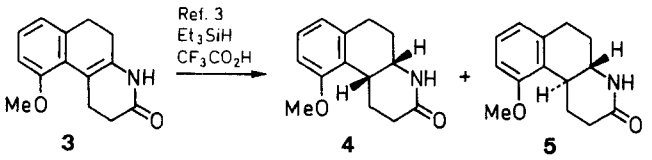
β-Tetralone pyrrolidine enamines **6** react with acrylamine to produce mixtures of double bond positional isomeric tetrahydrobenzo[*f*]quinolin-3(2*H*)-ones, e.g. **3**, **11**, **12**. Each of these isomers is reduced stereoselectively by triethylsilane–trifluoroacetic acid to the cis- or trans-fused octahydrobenzo[*f*]quinolone system, e.g. **4**, **5**. It is established that reported failures to prepare pure trans-fused product **5** by this reductive method is due to the heterogeneity of the product of the β-tetralone enamine–acrylamide reaction, and not to a defect in the reducing reagent system.

A prior communication[2] described stereospecific reduction of several A ring-substituted tetrahydrobenzo[*f*]-quinolones **1** to form exclusively the *trans*-hexahydrobenzo[*f*]quinolones **2** using a triethylsilane–trifluoroacetic acid reagent system.



1 **2**

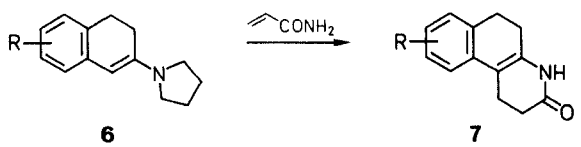
In contrast, Mellin et al.[3] found that reduction of the 10-methoxy-1,4,5,6-tetrahydrobenzo[*f*]quinolin-3(2*H*)-one **(3)** under the same reaction conditions afforded a 35:65 ratio of trans:cis-ring fused isomers **5** and **4**, thus challenging the claim of stereospecificity for the reduction method.



3 **4** **5**

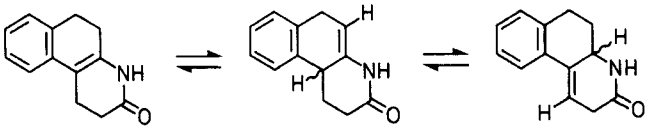
Work in our laboratory confirmed the lack of stereoselectivity in reduction of **3**, using a variety of experimental conditions, solvents, and of mono-, di- and trisubstituted silane derivatives.

Tetrahydrobenzo[*f*]quinolones **1** are synthesized by an aza-annulation reaction first described by Stork[4] and later modified by Ninomiya et al.[5] The procedure involves warming a β-tetralone pyrrolidine enamine **6** with excess acrylamide, followed by a brief period of heating at an elevated temperature to polymerize the excess acrylamide.



6 **7**

We speculated that the apparent stereochemical capriciousness of the reduction of the $\Delta^{4a,10b}$ double bond of 1,4,5,6-tetrahydrobenzo[*f*]quinolin-3(2*H*)-ones might be explainable on the basis of migration of this double bond to other position(s) in the ring system of **3** and related molecules. Tautomeric equilibria seem possible in the enamide structure **8**:

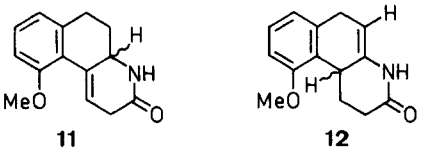


8 **9** **10**

The presence in the aza-annulation product of species such as **9** and **10** could explain the occasional formation of cis-ring fused product in a reduction that is reputed to proceed by trans-addition across the double bond. However, no mention of double bond enamide isomers in the aza-annulation reaction product was made in Ninomiya's[5] original paper, nor in subsequent studies[3,6] of benzoquinolines. Yan and Kozikowski[7] found double bond positional isomer products from an aza-annulation reaction of the pyrrolidine enamine of a cyclohexanone derivative with acrylamide.

The goal of the present study was to reinvestigate the Stork–Ninomiya aza-annulation reaction, to determine the chemical nature of the product(s) of the reaction, and to utilize the results of this investigation in gaining a better understanding of the stereochemical course of the triethylsilane–trifluoroacetic acid reduction.

1,2,3,4-Tetrahydro-8-methoxynaphthalen-2-one was subjected to conditions of the Ninomiya et al.[5] aza-annulation reaction. Radial thin layer chromatographic separation of the reaction products permitted the isolation of three isomeric compounds, subsequently identified as **3**, **11**, and **12**.



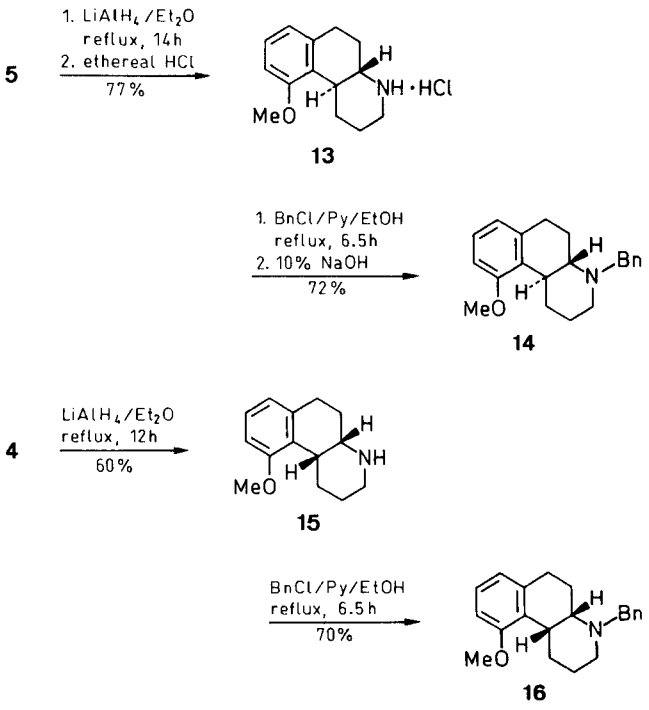
11 **12**

IR spectra of the three products revealed that two of them (subsequently assigned structures **3** and **12**) gave two strong bands in the region $\nu = 1640-1680\ cm^{-1}$, one of which is assignable to C=O, and the other to an enamide C=C stretch.[8] The other product (subsequently assigned

structure **11**) showed only one band (C=O) in the 1640–1680 cm^{-1} region. Initial ^1H NMR analysis revealed, in two of the three spectra, the presence of one signal in the olefinic region (δ = 6.17; δ = 5.21) integrating for one proton; these data are consistent with structures **11** and **12** and eliminate structure **3**. The downfield chemical shift of δ = 6.17 for the olefinic proton signal (as compared to the olefinic proton signal at δ = 5.21) was concluded to be consistent with structure **11**. The olefinic proton at position 1 of **11** forms a part of an extended conjugation system and it lies in proximity to the deshielding region of the methoxy at position 10. These two factors contribute to a downfield chemical shift value for this olefinic proton as compared to the olefinic proton at position 5 in **12**. Thus, the structures of the three isomeric products of the Stork–Ninomiya annulation could be assigned on the basis of spectral data. These assignments were confirmed by a series of high-field proton and ^{13}C NMR spectroscopic studies.

Because of the relative ease of separation of **3**, **11**, and **12** from the annulation reaction mixture and from each other, and their apparent stability at ambient temperature, it is concluded that a facile tautomeric equilibrium among the three structures is not operative.

The isomers **3**, **11**, and **12** were separately subjected to identical ionic reduction conditions with triethylsilane–trifluoroacetic acid. Pure **3** and **12** gave very high yields (> 90 %) of trans-fused product **5**, whereas **11** gave a similarly high yield of the cis-product **4**. The structures of these reduction products were verified by subsequent conversion to the known *cis*- and *trans*-*N*-benzyl-10-methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinolines **16** and **14** via **15** and **13**, respectively. The geometry of ring fusion was confirmed by NMR spectroscopy of these *N*-benzyl derivatives. The *N*-benzyl methylene protons (NCH_2Ph) of the trans-isomer **14** gave rise to doublets, whereas these protons in the cis-isomer **16** appeared as a singlet.[11]



The cis- and trans-lactams **4**, **5**, respectively, were first reduced with lithium aluminum hydride to the known cis-**15**[6] and trans-**13**[3] octahydrobenzo[*f*]quinolines. It is therefore established that, in the reduction of a mixture of the three isomers **3**, **11**, **12** isolated from the aza-annulation step (as performed in past studies in our laboratory and elsewhere[2]) reduction of **11** gave a cis-ring fused product, which had been interpreted as resulting from a non-stereospecific reduction of **3**.

The relative amounts of each olefinic isomer in the aza-annulation product determine the ratio of cis/trans reduction products produced. An incomplete study of influence of reaction conditions on isomeric olefinic product distribution generated conflicting data. The relative amount of acrylamide employed in the aza-annulation reaction was considerably greater than was used by the Ninomiya group.[5] The possible effect of this change on product distribution of isomeric enamides was not addressed.

A preparative aza-annulation procedure was devised, which provides as the principal products isomers **3** and **12**, both of which are reducable, via triethylsilane–trifluoroacetic acid, to the trans-ring fused product **5**. This procedure precludes the necessity of a chromatographic separation of the aza-annulation products; the isomeric product mixture can be used directly in the reduction step to provide trans-isomer **5** exclusively. Ionic reduction using triethylsilane and trifluoroacetic acid is stereoselective for the isomers **3**, **11**, and **12**.

Melting points were determined in open capillaries using a Thomas-Hoover Uni-Melt apparatus, and are uncorrected. IR spectra were recorded on a Nicolet 5DXB FT-IR instrument. NMR spectra were recorded on Bruker-IBM NR-80 or Bruker-IBM WM-360 spectrometers, using TMS as the internal standard. Mass spectra were recorded with a Ribermag R-10-10C mass spectrometer. Preparative chromatography was done either with a Chromatotron® apparatus (Harrison Research) using Kieselgel 60PF254 (EM Science) as the stationary phase or by flash chromatography using 150A, 35–75 μ silica gel. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. All new compounds gave satisfactory elemental analyses: C ± 0.31, H ± 0.18, N ± 0.02.

Annulation of 1,2,3,4-Tetrahydro-8-methoxynaphthalen-2-one; Formation of 10-Methoxy-1,4,5,6-tetrahydrobenzo[*f*]quinolin-3(2*H*)-one (3), 10-Methoxy-4,4a,5,6-tetrahydrobenzo[*f*]quinolin-3(2*H*)-one (11), and 10.Methoxy-1,4,6,10b-tetrahydrobenzo[*f*]quinolin-3(2*H*)-one (12):

To 1,2,3,4-tetrahydro-8-methoxynaphthalen-2-one[10] (3.1 g, 0.0176 mol) and TsOH (150 mg) in benzene (40 mL) was added, dropwise, freshly distilled pyrrolidine (1.77 g, 0.0249 mol) in benzene (10 mL), while the mixture was heated under reflux in a Dean-Stark apparatus. Heating was continued for 2 h, then the volatiles were distilled in a stream of N_2 under reduced pressure. Acrylamide (6.5 g, 0.118 mol) was added to the warm (50 °C) mixture and stirred at 80–85 °C for 1 h. The temperature was increased to 130 °C and this temperature was maintained for 25 min. To the hot mixture, H_2O (35 mL) was added and stirred vigorously for 10 min. Upon standing at r. t., a yellow solid separated from the H_2O layer. The H_2O layer was decanted and the solid was triturated with a small volume of acetone, collected on a filter, and washed twice with small volumes of cold (– 78 °C) acetone. TLC analysis (silica gel, $CHCl_3$–MeOH, 10:1) of the resulting white solid (0.44 g)

revealed that the solid was largely **3** (high R_f value component) with a small amount of **12** (low R_f value component). This material was dissolved in the acetone filtrate and this solution was evaporated under reduced pressure to afford a residue which was flash chromatographed on silica gel and eluted with hexanes/EtOAc (2:1) to afford 0.848 g (21%) of what was subsequently shown to be pure **3** and 0.702 g of a mixture of **3**, **11**, and **12**. This mixture was reserved as Fraction A.

Compound **3**: mp 182°C (acetone) [Lit.[6] mp 202–205°C (acetone–petroleum ether)].

IR (KBr): ν = 1680 (vs, C=O), 1644 cm^{-1} (vs, enamide C=C).

^1H NMR (360.13 MHz, $CDCl_3$): δ = 2.29 (t, 2H, H-5, J = 7.6 Hz), 2.53 (t, 2H, H-6, J = 7.6 Hz), 2.96 (t, 2H, H-1, J = 8 Hz), 3.77 (s, 3H, OCH_3), 6.75 (d, 2H, H-7, 9, J_{ortho} = 7.8 Hz), 7.8 (dd, 1H, H-8, J_{ortho} = 7.8 Hz), 8.9 (br s, 1H, NH).

^{13}C NMR (90 MHz): δ = 23.48 (C-1), 25.68 (C-5), 29.13 (C-6), 31.45 (C-2), 55.00 (OCH_3), 109.70 (C-10b), 110.47 (C-9), 120.30 (C-7), 123.29 (C-4a), 126.05 (C-8), 133.42 (C-10a), 136.21 (C-6a), 155.77 (C-10), 172.60 (C-3).

MS: m/z = 230 (M^+ + H).

Fraction A was subjected to Chromatotron® radial TLC (4 mm plate, hexanes/EtOAc, 2:1). The eluate was collected in 2 mL fractions, which permitted the isolation of pure **3** (first eluate), pure **11** (second eluate), and pure **12** (third eluate), in addition to fractions containing mixtures. Mixed fractions were pooled and recycled through the separation procedure. Pure fractions were individually pooled and evaporated under reduced pressure to afford solid material; compound **3**; 0.08 g (2%); mp 182°C (acetone).

Compound **11**: 0.180 g (5%); mp 209°C (acetone).

IR (KBr): ν = 1674 cm^{-1} (vs, C=O).

^1H NMR (360.13 MHz, $CDCl_3$): δ = 1.68 (m, 1H, H-5), 2.08 (m, 1H, H-5), 2.45 (m, 1H, H-6), 2.63 (m, 3H, H-4a, 6, 2), 2.86 (d, 1H, J = 7.2 Hz), H-2), 3.8 (s, 3H, OCH_3), 6.17 (s, 1H, H-1), 6.7 (2d, 2H, H-7, 9, J_{ortho} = 7.8 Hz), 7.0 (dd, 1H, H-8, J_{ortho} = 8.8 Hz), 8.8 (br s, 1H, NH).

MS: m/z = 229 (M^+).

Compound **12**: 0.082 g (2%); mp 193°C (acetone).

^1H NMR (360.13 MHz, $CDCl_3$): δ = 1.49–1.55 (m, 1H, H-2), 2.58–2.83 (m, 3H, H-2, 2×H-1), 3.41–3.59 (m, 3H, H-10b, 2×H-6), 3.78 (s, 3H, OCH_3), 5.21 (d, 1H, H-5, J = 3 Hz), 6.73 (d, 1H, H-9, J_{ortho} = 7.9 Hz), 6.75 (d, 1H, H-7, J_{ortho} = 7.9 Hz), 7.18 (dd, 1H, H-8, J_{ortho} = 7.9 Hz), 9.03 (br s, 1H, NH).

MS: m/z = 229 (M^+).

General Aza-annulation Procedure Affording a Mixture of 10-Methoxy-1,4,5,6-tetrahydrobenzo[*f*]quinolin-3(2*H*)-one (3) and 10-Methoxy-1,4,6,10b-tetrahydrobenzo[*f*]quinolin-3(2*H*)-one (12):

To a refluxing solution of 1,2,3,4-tetrahydro-8-methoxynaphthalen-2-one[10] (3 g, 0.017 mol) and TsOH (175 mg) in benzene (40 mL) in a Dean-Stark apparatus was added, dropwise, freshly distilled pyrrolidine (2 g, 0.028 mol) in benzene (5 mL). Heating was continued until H_2O ceased to form (0.5–1 h), then volatiles were distilled in a N_2 stream under reduced pressure. Acrylamide (4.5 g, 0.082 g) was added to the warm (ca. 65°C) mixture, and stirred at 76–80°C for 2 h. H_2O (25 mL) was then added and stirred for 10 min. On standing at r.t., a yellow solid separated from the aqueous layer, which was decanted. The yellow solid was collected on a filter, then treated with several portions of Et_2O, each of which was immediately placed in a separatory funnel and washed with H_2O. The pooled Et_2O extracts were evaporated under reduced pressure to ca. 20 mL. The resulting precipitate was collected on a filter to afford 1.2 g (30%) of an off-white solid whose TLC analysis (silica gel, hexanes/EtOAc, 1:1) revealed only two components **3** and **12**.

***trans*-10-Methoxy-1,4,4a,5,6,10b-hexahydrobenzo[*f*]quinolin-3(2*H*)-one (5):**

A mixture of **3** (0.67 g, 0.00292 mol) and Et_3SiH (1.00 g, 0.008 mol) in CH_2Cl_2 (5 mL) was stirred for 10 min. CF_3CO_2H (2.5 mL, 0.0325 mol) was added dropwise with stirring, and the mixture was stirred for 8 h at r.t. The mixture was neutralized with 10% Na_2CO_3 and extracted with CH_2Cl_2 (3 × 20 mL). The pooled extracts were washed with H_2O and the volatiles were removed under reduced pressure to afford an oily residue which, after treatment with Et_2O, gave 0.632 g (94%) of a white solid homogeneous by TLC analysis (silica gel, CH_2Cl_2–THF–MeOH, 3:2:0.04); mp 219.5–221.5°C.

^1H NMR (360.13 MHz, $CDCl_3$): δ = 1.75 (m, 1H, H-1), 1.95 (m, 2H, H-5), 2.25 (m, 1H, H-1), 2.55 (m, 2H, H-2), 2.85 (m, 2H, H-6), 3.35 (m, 1H, H-10b), 3.65 (m, 1H, H-4a), 3.80 (s, 3H, OCH_3), 6.70 (2 d, 2H, H-7,9), 7.20 (dd, 1H, J = 6.4 Hz, H-8).

^{13}C NMR (90 MHz): δ = 23. 4(C-1), 27.7 (C-5), 28.5 (C-2), 31.7 (C-6), 31.9 (C-10b), 51.6 (C-4a), 55.2 (OCH_3), 107.5 (C-9), 121.0 (C-7), 126.3 (C-10a), 126.9 (C-8), 136.3 (C-6a), 157.4 (C-10), 172.4 (C-3).

***cis*-10-Methoxy-1,4,4a,5,6,10b-hexahydrobenzo[*f*]quinolin-3(2*H*)-one (4):**

A mixture of **11** (340 mg, 1.48 mmol) and Et_3SiH (50 mg, 4.3 mmol) in CH_2Cl_2 (2.5 mL) was stirred for 10 min. CF_3CO_2H (1.25 mL, 0.016 mol) was added dropwise with stirring, and the resulting mixture was stirred for 8 h at r.t. The mixture was neutralized with 10% Na_2CO_3 and extracted with CH_2Cl_2 (3 × 20 mL). The pooled extracts were washed with H_2O, and the volatiles were evaporated under reduced pressure. The oily residue was treated with Et_2O to form 0.308 g (90%) of a white solid; mp 175–178°C. This material showed one spot on TLC analysis (silica gel CH_2Cl_2–THF–MeOH, 3:2:0.04).

^1H NMR (360.13 MHz, $CDCl_3$): δ = 1.65 (m, 1H, H-10b), 1.95 (m, 1H), 2.40 (m, 2H), 2.50 (m, 2H), 2.60 (m, 1H), 2.81 (m, 1H), 3.22 (m, 1H, H-6), 3.25 (m, 1H, H-4a), 3.78 (s, 3H, OCH_3), 6.69 (d, 1H, J = 7.4 Hz, H-7), 6.71 (d, 1H, J = 7.4 Hz, H-9), 7.07 (dd, 1H, J = 6.8 Hz, H-8).

^{13}C NMR (90 MHz): δ = 28.3, 32.2, 32.4, 36.3, 36.8 (C-10b), 56.0 (C-4a), 56.0 (OCH_3), 109.0 (C-9), 122.6 (C-7), 124.3, 128.7 (C-8), 138.6, 159.6 (C-10), 175.8 (C-3).

MS: m/z = 231 (M^+).

***trans*-10-Methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline Hydrochloride (13):**

A mixture of **5** (0.900 g, 0.0039 mol) and $LiAlH_4$ (0.450 g, 0.0116 mol) in anhydr. Et_2O (150 mL) was stirred under reflux for 14 h. Excess $LiAlH_4$ was destroyed by dropwise addition of aq NaK tartrate (0.9 g/mL) to the chilled (0°C), stirred mixture over 0.75 h or until evolution of H_2 ceased. The metallic salts were removed by filtration and the filtrate was washed with H_2O and dried (Na_2SO_4). Volatiles were removed under reduced pressure and the residual oil was treated with ethereal HCl to afford a pale yellow solid. This material was crystallized from a mixture of MeOH and Et_2O to afford 0.76 g (77%) of a pale yellow solid; mp 262–263°C (Lit.[3] mp 266–268°C).

MS: m/z = 217 (M^+).

***trans*-*N*-Benzyl-10-methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]-quinoline (14):**

A mixture of **13** (91 mg, 0.42 mmol), benzyl chloride (80 mg, 0.63 mmol), and pyridine (3 mg, 0.38 mmol) in abs. EtOH (10 mL) was stirred and heated under reflux for 6.5 h. The cooled mixture was made basic with 10% NaOH and extracted with CH_2Cl_2 (3 × 20 mL). The pooled organic extracts were evaporated to afford an oily residue which was chromatographed on a Chromatotron® apparatus and eluted with $CHCl_3$-MeOH (20:1) to afford 93 mg (72%) of an opaque oil.

A small amount of this material was treated with ethereal HCl and the resulting solid was recrystallized from MeOH – Et_2O to afford the hydrochloride of **14** as a white solid; mp 244–245°C (Lit.[3] mp 256–258°C).

^1H NMR (free base) ($CDCl_3$): δ = 3.69 (d, 1H, ArCH'H, J_{gem} = 13.4 Hz), 3.83 (d, 1H, ArCH'H, J_{gem} = 13.4 Hz).

***cis*-10-Methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (15):**
A mixture of **4** (0.130 g, 0.000563 mol) and $LiAlH_4$ (0.007 g, 0.0018 mol) in anhydr. Et_2O (50 mL) was stirred and heated under reflux for 12 h. Excess $LiAlH_4$ was destroyed by dropwise addition of aq NaK tartrate (0.9 g/mL) to the chilled (0 °C), stirred mixture until evolution of H_2 ceased. The mixture was filtered and the filtrate washed with H_2O and dried (Na_2SO_4). Volatiles were removed under reduced pressure and the residual gold oil was chromatographed on silica gel and eluted with $CHCl_3$–MeOH–conc. NH_4OH (5:0.5:0.04) to afford 0.395 g (60%) of a clear oil.

MS: $m/z = 217$ (M^+).

***cis*-*N*-Benzyl-10-methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (16):**
A mixture of **15** (0.050 g, 0.00023 mol), benzyl chloride (0.0724 g, 0.00043 mol), and pyridine (0.030 g, 0.00038 mol) in abs. EtOH (10 mL) was treated as described for **14**. Yield of eluate from Chromatotron® separation: 0.048 g (70%) of an opaque oil.

A small amount of this material was treated with ethereal HCl and the resulting solid was recrystallized from MeOH–Et_2O to afford the hydrochloride of **16** as a white solid; mp 253–253.5 °C (Lit.[6] mp 250–253 °C).

^1H NMR (free base) ($CDCl_3$): $\delta = 3.73$ (s, 1 H, ArCH′H), 3.76 (s, 1 H, ArCH′H).

(1) Abstracted from a portion of a thesis submitted by K.S.K. in partial fulfillment of the requirements for the Ph.D. degree, University of Iowa, 1992.
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