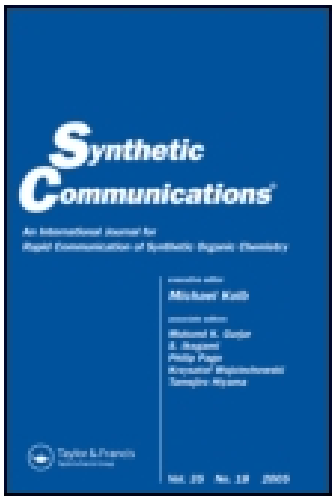


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

NEW 6-ETHOXYQUINOLINES AS SIMPLE OPTOQUINE ANALOGUES

Raymond C. F. Jones [a] , Russell J. Collighan [b] , Joanna Crane [b] , Nikolas J. Hodges [b] , Matthew S. Ling [b] & Joanne Stroud [b]

[a] Department of Chemistry , Loughborough University , Loughborough, Leics, LE11 3TU, UK

[b] Department of Chemistry , Nottingham University , Nottingham, NG7 2RD, UK

Published online: 16 Aug 2006.

To cite this article: Raymond C. F. Jones , Russell J. Collighan , Joanna Crane , Nikolas J. Hodges , Matthew S. Ling & Joanne Stroud (2002) NEW 6-ETHOXYQUINOLINES AS SIMPLE OPTOQUINE ANALOGUES, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 32:20, 3185-3191, DOI: 10.1081/SCC-120013738

To link to this article: http://dx.doi.org/10.1081/SCC-120013738

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

SYNTHETIC COMMUNICATIONS
Vol. 32, No. 20, pp. 3185–3191, 2002

NEW 6-ETHOXYQUINOLINES AS SIMPLE OPTOQUINE ANALOGUES

Raymond C. F. Jones,* Russell J. Collighan, Joanna Crane, Nikolas J. Hodges, Matthew S. Ling, and Joanne Stroud

Department of Chemistry, Nottingham University, Nottingham NG7 2RD, UK

ABSTRACT

Reaction of 6-ethoxylepidine (6-ethoxy-4-methylquinoline) with strong base and electrophiles leads to new derivatives, as possible optoquine analogues.

Key Words: Optoquine; 6-Ethoxyquinolines; 6-Ethoxylepidine

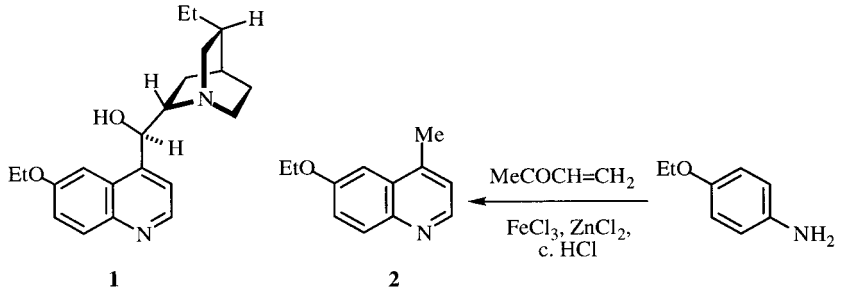
The pneumococcus is a major pathogen of man, responsible for as many as 30,000 deaths per annum from a variety of diseases including pneumonia, bacterial meningitis, septic arthritis and septicaemia. The sensitivity of pneumococcus to optoquine **1** is used to differentiate pneumococcus from low grade pathogens. Although effective antibiotic treatments for pneumococcal infections exist, there is interest in the role of optoquine

*Corresponding author. Current address: Department of Chemistry, Loughborough University, Loughborough, Leics, LE11 3TU, UK. Fax: +44 1509 223926; E-mail: r.c.f.jones@lboro.ac.uk

DOI: 10.1081/SCC-120013738 0039-7911 (Print); 1532-2432 (Online)

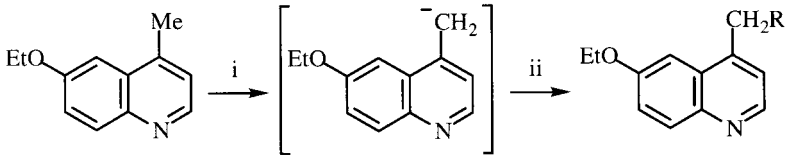
in vivo, and as a new lead to an antipneumococcal drugs.[1] Prompted by the scant attention paid in the literature to 6-ethoxyquinolines, we report here our studies on much simplified structures related to the quinoline portion of optoquine and in particular to 6-ethoxylepidine (6-ethoxy-4-methylquinoline; **2**), which has been found to retain some (approx. 1%) of the biological activity of optoquine **1**.[2]

6-Ethoxylepidine **2** was prepared in low isolated yield (13%) but on a multigram scale, after an extensive purification sequence, from 4-ethoxyaniline and but-3-en-2-one using a procedure reported for the 6-methoxy analogue ($FeCl_3$, $ZnCl_2$, conc. HCl, EtOH).[3]



1 **2**

Our strategy was to modify the C(4)-methyl group of **2**, including elaboration to incorporate a heteroatom, by utilising its potential for deprotonation to anion **3**.[4] Thus treatment of 6-ethoxylepidine **2** with lithium diisopropylamide followed by an electrophile (THF, $-78 \rightarrow 20^{\circ}C$) afforded the new derivatives **4a–f** after reaction with iodoethane, ethanal, propanone, benzaldehyde, 2-naphthaldehyde and pyridine-2-aldehyde, respectively



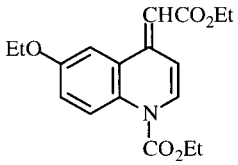
2 **3**

4a; R = $MeCH_2$
4b; R = MeCH(OH)
4c; R = $Me_2C(OH)$
4d; R = PhCH(OH)
4e; R = (2-naphthyl)CH(OH)
4f; R = (2-pyridyl)CH(OH)

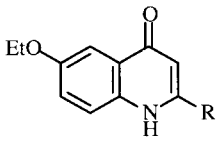
Scheme 1. Reagents: i, LDA, THF, $-78^{\circ}C$; ii, electrophile (EtI, MeCHO, Me_2CO, PhCHO, 2-naphthaldehyde, or pyridine-2-aldehyde), $-78 \rightarrow 20^{\circ}C$.

(Sch. 1). Quantities of starting material **2** were detected in the crude reaction products, and it is possible that some of the carbonyl additions are reversible, with adducts reverting on warming to room temperature before quenching. Attempted alkylations with *N*-bromomethyl- and *N*-(3-bromopropyl)phthalimide, and additions to 3-quinuclidone and to the imine benzylidene aniline, did not afford products under these conditions. Acylation with ethyl chloroformate led to isolation of the *N*,*C*-diacylated material **5** along with recovered starting material **2**.

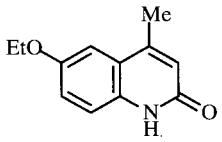
In addition to compounds **4a–f**, we also prepared three new 6-ethoxyquinolones. The 4-quinolone **6a** was accessed by pyrolysis of the enaminoester formed from 4-ethoxyaniline and methoxymethylene Meldrum's acid;[5] both solution[5] and flash vacuum methods[6] were successful. The 2-methyl-4-quinolone **6b** and 4-methyl-2-quinolone **7** were prepared by treatment of 4-ethoxyaniline with ethyl acetoacetate (20°C, 48 h, or 120–140°C, 30 min, respectively) followed by acidic cyclisation.[7] The 4-quinolones have a C(4)-hetero substituent and the C(4) methyl group in **7** has potential for elaboration.



5



6 a; R = H
b; R = Me



7

All of the above compounds were subjected to preliminary screening for anti-pneumococcal activity; increased activity over that of 6-ethoxylepidine **2** was indicated by the 4-(2-phenyl-2-hydroxyethyl) adduct **3d**, which had activity at 12% of that of optoquine.

EXPERIMENTAL

Melting points (uncorrected) was determined on a Gallenkamp capillary apparatus. IR spectra were recorded on a Perkin-Elmer 1600 series FTIR spectrometer, mass spectra using a VG70E spectrometer, and ^{1}H NMR spectra using a Bruker WM 250 instrument at 250 MHz unless otherwise stated. Column chromatography was carried out under medium pressure using Merck Kieselgel 60 silica gel (Art. 7729), and TLC using silica plates, Camlab SilG/UV_{254}. Organic solutions were dried with $MgSO_4$.

6-Ethoxy-4-methylquinoline 2: 4-Ethoxyaniline (79.9 g, 0.58 mol), iron(III) chloride hexahydrate (251.9 g, 0.93 mol), anhydrous zinc chloride (10.0 g), ethanol (450 cm^3) and conc. hydrochloric acid (57 cm^3) were heated together to 60–65°C with stirring before the dropwise addition over 1 h of but-3-en-2-one (38.8 cm^3, 32.6 g, 0.46 mol). The mixture was then heated at reflux for 3 h, left to stand overnight, and the ethanol removed under reduced pressure. The residue was basified with aqueous sodium hydroxide (25% w/v) and the mixture filtered through kieselguhr, to remove black tarry solids, and extracted with ether. The ether extracts, combined with the ether solution obtained by repeated washing of the black solids, were dried, filtered and evaporated under reduced pressure. The residual brown oil was distilled under reduced pressure, collecting the fraction b.p. 90–120°C at 1.5 mm Hg as an oil which solidified to a yellow–white solid. Final purification by kugelrohr distillation afforded the title compound **2** as an off-white crystalline solid (11.2 g, 13%), m.p. 62–65°C (Found: M^+ 187.098. $C_{12}H_{13}NO$ requires: *M* 187.100); ν_{max}: $(CHCl_3)/cm^{-1}$ 3260, 2942, 1622, 1596, 1363; $\delta(CHCl_3)$ 1.50 (3H, t, *J* 7 Hz, CH_3CH_2O), 2.64 (3H, s, 4-CH_3), 4.17 (2H, q, *J* 7 Hz, CH_3CH_2O), 7.20 (2H, m, 3-H, 5-H), 7.60 (1H, dd, *J* 2.5, 9 Hz, 7-H), 8.00 (1H, d, *J* 9 Hz, 8-H), 8.62 (1H, d, *J* 4 Hz, 2-H); *m*/*z* 187 (M^+).

General method for preparation of 4-substituted 6-ethoxyquinolines 4a–f: To 6-ethoxy-4-methylquinoline **2** (0.5 g, 2.7 mmol) in dry THF (20 cm^3) at −78°C under nitrogen was added lithium diisopropylamide (4 mmol, as a solution in THF–hexanes). The mixture was stirred at −78°C for 30 min before addition of the electrophile (3 mmol). After stirring for a further 15 min, the mixture was allowed to warm to room temperature, poured into saturated brine (20 cm^3) and extracted with diethyl ether (2 × 25 cm^3). The ethereal extracts were dried, the solvents removed under reduced pressure, and the residue was purified by column chromatography, eluting with chloroform : methanol (99 : 1 v/v) or ethyl acetate : hexane : triethylamine (40 : 55 : 5 v/v/v) to afford the title compounds. When ethyl chloroformate was used as electrophile (with R. VIPOND), a compound was isolated in low yield that was assigned as the *N*,*C*-diacylated material **5** from its ^1H NMR spectrum, which displayed signals for three ethoxy groups along with the remainder of the expected pattern.

6-Ethoxy-4-propylquinoline 4a: Prepared using iodoethane as electrophile, as a waxy white solid (41%) (Found: M^+ 215.131. $C_{14}H_{17}NO$ requires *M* 215.131); ν_{max} $(CHCl_3)/cm^{-1}$ 3196, 2934, 2824, 1698, 1621, 1592, 1462, 1316; δ $(CHCl_3)$ 1.04 (3H, t, *J* 8 Hz, $CH_3CH_2CH_2$), 1.49 (3H, t, *J* 7 Hz, CH_3CH_2O), 1.75 (2H, m, $CH_3CH_2CH_2$), 2.95 (2H, m, $CH_3CH_2CH_2$), 4.10 (2H, q, *J* 7 Hz, CH_3CH_2O), 7.40 (3H, m, ArH), 8.20 (1H, d, *J* 8 Hz, 8-H), 8.80 (1H, d, *J* 4 Hz, 2-H); *m*/*z* 215 (M^+), 187, 172, 170, 159, 128.

6-Ethoxy-4-(2-hydroxypropyl)quinoline 4b: Prepared using ethanal as electrophile, as a waxy white solid (27%) (Found: M^+ 231.126. $C_{14}H_{17}NO_2$ requires *M* 231.126); ν_{max} ($CHCl_3$)/cm^{-1} 3314, 2933, 1621, 1592, 1403; δ ($CHCl_3$) 1.42 (3H, d, *J* 7 Hz, C*H*$_3$CH), 1.50 (3H, t, *J* 7 Hz, C*H*$_3$CH$_2$O), 2.45 (1H, br, s, OH), 3.40 (2H, d, *J* 8 Hz, C*H*$_2$CH), 4.20 (3H, m, CH$_3$C*H*$_2$O, C*H*OH), 7.3 (3H, m, ArH), 8.05 (1H, d, *J* 8 Hz, 8-H), 8.60 (1H, d, *J* 4 Hz, 2-H); *m*/*z* 231 (M^+), 198, 187, 180, 172, 127.

6-Ethoxy-4-(2-hydroxy-2-methylpropyl)quinoline 4c: Prepared using propanone as electrophile, as a waxy white solid (38%) (Found: M^+ 245.143, $C_{15}H_{19}NO_2$ requires *M* 245.142); ν_{max} ($CHCl_3$)/cm^{-1} 3285, 2943, 1621, 1593; δ ($CHCl_3$) 1.32 (6H, s, 2 × CH$_3$C), 1.48 (3H, t, *J* 7 Hz, C*H*$_3$CH$_2$O), 1.73 (1H, br, s, OH), 3.22 (2H, s, CH$_2$C), 4.17 (2H, q, *J* 7 Hz, CH$_3$C*H*$_2$O), 7.30 (3H, m, ArH), 8.04 (1H, d, *J* 8 Hz, 8-H), 8.06 (1H, d, *J* 4 Hz, 2-H); *m*/*z* 245 (M^+), 213, 201, 187, 172.

6-Ethoxy-4-(2-hydroxy-2-phenylethyl)quinoline 4d: Prepared using benzaldehyde as electrophile, as a white solid, m.p. 138–140°C (56%) (Found: C, 77.58; H, 6.66; N, 4.71%. $C_{19}H_{19}NO_2$ requires: C, 77.79; H, 6.53; N, 4.77%); ν_{max} ($CHCl_3$)/cm^{-1} 3447, 1621, 1463; δ ($CHCl_3$) 1.47 (3H, t, *J* 7 Hz, C*H*$_3$CH$_2$O), 2.44 (1H, br, s, OH), 3.40 (2H, d, *J* 8 Hz, C*H*$_2$CH), 4.10 (2H, q, *J* 7 Hz, CH$_3$C*H*$_2$O), 5.10 (1H, t, *J* 8 Hz, CHOH), 7.15–7.40 (8H, m, ArH), 7.90 (1H, d, *J* 9 Hz, 8-H), 8.30 (1H, d, *J* 4.5 Hz, 2-H); *m*/*z* 293 (M^+), 187, 172, 158.

6-Ethoxy-4-[2-hydroxy-2-(2-naphthyl)ethyl]quinoline 4e: Prepared using 2-naphthaldehyde as electrophile (26%) (Found C, 80.58; H, 6.22; N, 4.29%. $C_{23}H_{21}NO_2$ requires: C, 80.44; H, 6.16; N, 4.08%); δ ($CHCl_3$) 1.43 (3H, t, *J* 7 Hz, C*H*$_3$CH$_2$O), 3.78 and 3.90 (each 1H, dd, *J* 2.5 and 8 Hz, C*H*$_2$CH), 4.05 (2H, q, *J* 7 Hz, CH$_3$C*H*$_2$O), 5.45 (1H, t, *J* 8 Hz, C*H*OH), 7.30–7.80 (10H, m, ArH), 8.10 (1H, d, *J* 9 Hz, 8-H), 8.60 (1H, d, *J* 5.5 Hz, 2-H), 11.05 (1H, br, s, OH).

6-Ethoxy-4-[2-hydroxy-2-(2-pyridyl)ethyl]quinoline 4f: Prepared using pyridine-2-aldehyde as electrophile (10%) (Found C, 73.16; H, 6.26; N, 9.71%. $C_{18}H_{18}N_2O_2$ requires: C, 73.45; H, 6.16; N, 9.52%); δ ($CHCl_3$) 1.50 (3H, t, *J* 7 Hz, C*H*$_3$CH$_2$O), 3.52 (2H, d, *J* 8 Hz, C*H*$_2$CH), 4.22 (3H, m, CH$_3$C*H*$_2$O, OH), 5.18 (1H, t, *J* 8 Hz, C*H*OH), 7.0–7.7 (7H, m, ArH), 8.05 (1H, d, *J* 9.5 Hz, 8-H), 8.6 (1H, d, *J* 5 Hz, 2-H), 11.05 (1H, s, OH).

6-Ethoxy-4-quinolone 6a: (in part with J. JENKIN and M. E. JOHNSON) To methoxymethylene Meldrum's acid[5] (5.00 g, 0.027 mol) in dry acetonitrile (50 cm^3) was added freshly distilled 4-ethoxyaniline (3.83 g, 0.028 mol) and the mixture heated under reflux for 8 h before cooling to 0°C. The bright yellow solid was collected by filtration, washing with cold methanol, to afford (4-ethoxyphenyl)aminomethylene Meldrum's acid, m.p.

155–156°C (7.27 g, 92%) (Found: C, 61.76; H, 6.01; N, 5.07%. $C_{19}H_{17}N_3O$ requires: C, 61.85; H, 5.88; N, 4.81%); ν_{max} ($CHCl_3$)/cm^{-1} 3186, 2927, 1721, 1681, 1625, 1519, 1587 and 1459; δ ($CDCl_3$) 1.43 (3H, t, *J* 7 Hz, C*H*$_3$CH$_2$O), 1.75 (6H, s, 2 × CH_3), 4.04 (2H, q, *J* 7 Hz, CH_3C*H*$_2$O), 6.93 and 7.17 (each 2H, d, *J* 9 Hz, ArH), 8.53 (1H, d, *J* 14 Hz, C*H*NH), 11.22 (1H, d, *J* 14 Hz, CHN*H*). (4-Ethoxyphenyl)aminomethylene Meldrum's acid (0.5 g, 1.72 mmol) was heated at reflux (sand bath) in freshly distilled diphenyl ether (2 g) for 15 min. Addition of light petroleum (b.p. 40–60°C) to the cooled solution failed to precipitate any material, so chloroform was added to the light petroleum : diphenyl ether mixture, when a solid was obtained which was filtered and washed with further chloroform. The filtrate volume was reduced under reduced pressure, and the precipitation repeated twice. The title compound **6a** was obtained as a pale brown powdery solid (0.12 g, 37%), m.p. 249–254°C (Found: M^+ 189.078. $C_{11}H_{11}NO_2$ requires: *M* 189.079); ν_{max} ($CHCl_3$)/cm^{-1} 3272, 2931, 1621, 1580, 1564, 1129, 1114; δ (270 MHz; $CDCl_3$) 1.51 (3H, t, *J* 7 Hz, C*H*$_3$CH$_2$O), 4.14 (2H, q, *J* 7 Hz, CH_3C*H*$_2$O), 7.11 (1H, d, *J* 6.5 Hz, 3-H), 7.43 (1H, d, *J* 2.5 Hz, 5-H), 7.55 (1H, dd, *J* 2.5 and 9 Hz, 7-H), 7.83 (1H, d, *J* 9 Hz, 8-H), 8.30 (1H, d, *J* 6.5 Hz, 2-H), 10.1 (1H, br, s, NH); δ (270 MHz; d_6-DMSO) 1.36 (3H, t, *J* 7 Hz, C*H*$_3$CH$_2$O), 4.08 (2H, q, *J* 7 Hz, CH_3C*H*$_2$O), 6.01 (1H, d, *J* 7 Hz, 3-H), 7.30 (1H, dd, *J* 3 and 9 Hz, 7-H), 7.5 (2H, m, 5-H, 8-H), 7.85 (1H, d, *J* 7 Hz, 2-H), 11.75 (1H, br, s, NH). Flash vacuum pyrolysis of the arylidene Meldrum's acid (300 mg) by heating the sample to 158°C under high vacuum (10^{-4} mbar) before passing the vapour through a tube heated at 650°C, also afforded **6a** (76 mg, 35%), identical to that isolated from the solution pyrolysis, as a yellow–sandy deposit on a liquid nitrogen-cooled trap.

2-Methyl-4-quinolone 6b and 4-methyl-2-quinolone 7: (with A. FREEBURY and A. T. YATES) 4-Ethoxyaniline (15 g, 0.109 mol) was added to ethyl acetoacetate (60 cm^3) over 30 min and the mixture left at 20°C for 48 h. The precipitate was collected by filtration, washed with hexane and recrystallised to afford ethyl 3-(4-ethoxyphenyl)aminobut-2-enoate (16.22 g, 60%), m.p. 46–47°C (from ethanol) (Found: C, 67.60; H, 7.77; N, 5.57%. $C_{14}H_{19}NO_3$ requires: C, 67.45; H, 7.68; N, 5.62%); ν_{max} ($CHCl_3$)/cm^{-1} 3304, 2990, 2931, 1713, 1650, 1613, 1552, 1510, 1162, 1117; δ ($CDCl_3$) 1.25 and 1.40 (each 3H, t, *J* 7 Hz, C*H*$_3$CH$_2$O), 1.91 (3H, s, CH_3C), 4.05 and 4.15 (each 2H, q, *J* 7 Hz, CH_3C*H*$_2$O), 4.65 (1H, s, CH), 6.85 and 7.00 (each 2H, d, *J* 9 Hz, ArH), 10.15 (1H, s, NH). This enamino-ester (15.22 g, 0.061 mol) was added to conc. sulphuric acid (30 cm^3) over 30 min, keeping the temperature below 35°C. The mixture was heated to 90–95°C for 1 h, cooled, poured into ice-water and the precipitate collected by filtration, washed with water, then suspended in water. The suspension

was neutralised with aqueous ammonia, filtered and the precipitate washed with water and dried to afford the title compound **6b** (7.08 g, 57%), m.p. >230°C (from methanol) (Found: M^+ 203.095. $C_{12}H_{13}NO_2$ requires *M* 203.095); ν_{max} (Nujol)/cm^{-1} 3250, 2924, 1615; δ ($CDCl_3$) 1.37 (3H, t, *J* 7 Hz, CH_3CH_2O), 2.37 (3H, s, CH_3C), 4.12 (2H, q, *J* 7 Hz, CH_3CH_2O), 6.37 (1H, s, 3-H), 7.20 (3H, m, ArH), NH not observed. 4-Methyl-2-quinolone **7** was prepared as above from 4-ethoxyaniline and ethyl acetoacetate, but heating for 2 h at 120–140°C, to afford *N*-(4-ethoxyphenyl)-3-oxobutanamide (17.2 g, 71%), m.p. 88–90°C (Found: C, 65.44; H, 7.00; N, 6.32%. $C_{12}H_{15}NO_3$ requires: C, 65.14; H, 6.83; N, 6.33%); ν_{max} ($CHCl_3$)/cm^{-1} 3305, 2930, 1713, 1647, 1598, 1556; δ ($CDCl_3$) 1.39 (3H, t, *J* 7 Hz, CH_3CH_2O), 2.30 (3H, s, CH_3CO), 3.54 (2H, s, $COCH_2CO$), 4.00 (2H, q, *J* 7 Hz, CH_3CH_2O) 6.81 and 7.40 (each 2H, d, *J* 9 Hz, ArH), 9.03 (1H, s, NH). The amide (16.2 g, 0.073 mol) was cyclised as above to afford the title compound **7** (9.73 g, 65%), m.p. 215–217°C (from methanol) (Found: M^+ 203.094. $C_{12}H_{13}NO_2$ requires *M* 203.095); ν_{max} (Nujol)/cm^{-1} 3245, 2924, 1644, 1620, 1463; δ ($CDCl_3$) 1.35 (3H, t, *J* 7 Hz, CH_3CH_2O), 2.40 (3H, s, CH_3C), 4.05 (2H, q, *J* 7 Hz, CH_3CH_2O), 6.41 (1H, s, 3-H), 7.20 (3H, m, ArH), NH not observed.

ACKNOWLEDGMENTS

We thank Dr. A. R. Mellersh (Derby City Hospital) for biological data and financial assistance, and Parke-Davis Neuroscience Research Unit for partial financial support (M. S. L.).

REFERENCES

1. Mair, W.; Macleod, J.W.; Griffith, F.W. *A System of Bacteriology*; Medical Research Council, HMSO: London, 1929.
2. Mellersh, A.R. Derby City Hospital UK, personal communication.
3. Campbell, K.N.; Schaffner, I.J. J. Am. Chem. Soc. **1945**, *67*, 86.
4. Gutzwiller, J.; Uskokovic, M. J. Am. Chem. Soc. **1970**, *92*, 204.
5. Cassis, R.; Tapia, R.; Valderrama, J. A. Synth. Commun. **1985**, *15*, 125.
6. Gordon, H.J.; Martin, J.C.; McNab, H. J. Chem. Soc., Chem. Commun. **1983**, 957.
7. Mehrotra, S.; Barthwhal, J.P.; Pandey, B.R.; Bhargava, K.P.; Parmar, S.S. J. Heterocycl. Chem. **1980**, *17*, 1213.

Received in the USA October 29, 2001

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016