Chemistry of Natural Compounds and Bioorganic Chemistry

Synthesis of *N*-phenyl-substituted derivatives of morphine alkaloids

*S. K. Moiseev,[a] I. V. Bakhanova,[a] H. Schmidhammer,[b] and V. N. Kalinin[a]**

[a]*A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 28 ul. Vavilova, 117813 Moscow, Russian Federation. Fax: +7 (095) 135 6549. E-mail: vkalin@ineos.ac.ru*
[b]*Institute of Pharmaceutical Chemistry, University of Innsbruck, Innrain 52a, A-6020 Innsbruck, Austria. Fax: +43 (512) 507 2940*

A method for the preparation of *N*-phenyl-substituted morphine alkaloids by treatment of the corresponding *N*-nor derivatives with Ph_3Bi in the presence of $Cu(OAc)_2$ is proposed. 17-Nor-17-phenylthebaine thus obtained can serve as a convenient starting material for the preparation of other *N*-phenyl-substituted alkaloids.

Key words: thebaine, morphine alkaloids, arylation, triphenylbismuth.

The nature of the substituent at the nitrogen atom in morphine alkaloids is a significant factor having both quantitative and qualitative influence on their pharmacological activity.[1a] Recently we synthesized the first *N*-aryl substituted morphine alkaloid by introducing a phenyl group into the corresponding *N*-nor derivative on treatment with (η^6-fluorobenzene)chromiumtricarbonyl complex in the presence of K_2CO_3 in a THF—acetonitrile (1 : 1) mixture followed by elimination of the chromiumtricarbonyl group.[2] In the present study, we describe a more general way to *N*-phenyl-substituted morphine alkaloids, which involves either arylation of *N*-nor derivatives by Ph_3Bi or the use of the *N*-phenyl derivatives thus obtained as the starting compounds for subsequent transformations.

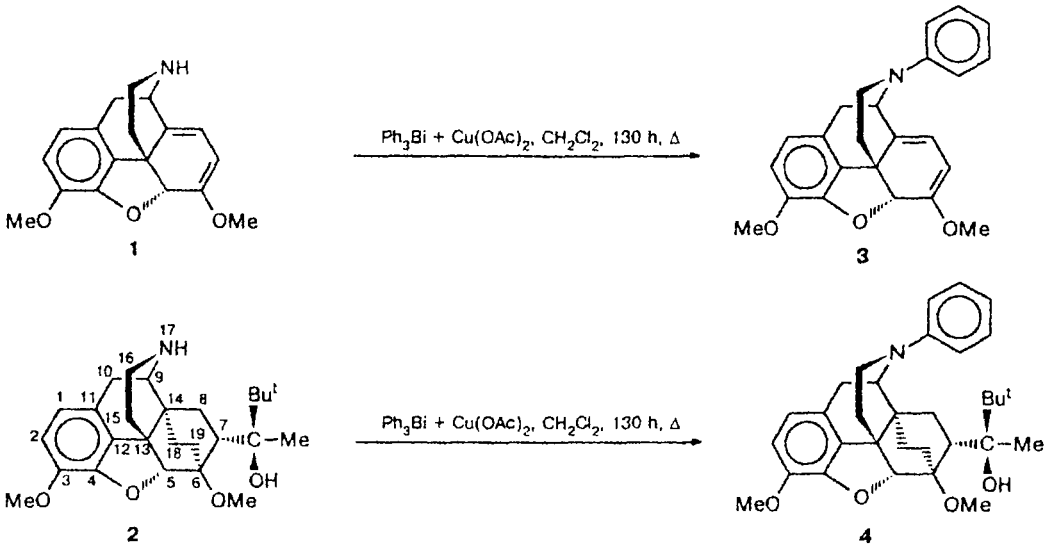
It is known that the amines containing an N—H bond are phenylated by Ph_3Bi in the presence of copper(II) acetate or trifluoroacetate at the nitrogen atom.[3] We have found that 17-northebaine[4] (**1**) and (6*R*,7*R*,14*S*)-7-[(2*S*)-2-hydroxy-3,3-dimethylbut-2-yl]-6,7,8,14-tetrahydro-6,14-ethano-17-northebaine[5] (**2**) are phenylated by Ph_3Bi upon prolonged refluxing in CH_2Cl_2 in the presence of $Cu(OAc)_2$ to give 17-phenyl-17-northebaine (**3**) and (6*R*,7*R*,14*S*)-7-[(2*S*)-2-hydroxy-3,3-dimethylbut-2-yl]-17-phenyl-6,7,8,14-tetrahydro-6,14-ethano-17-northebaine (**4**), respectively (Scheme 1).

It can be suggested that compound **3**, being an analog of the natural alkaloid thebaine (**5**) (Scheme 2), an important starting compound in the synthesis of derivatives of morphine alkaloids,[1b] would enter into the

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 3, pp. 595—598, March, 1999

1066-5285/99/4803-0589 $22.00

Scheme 1

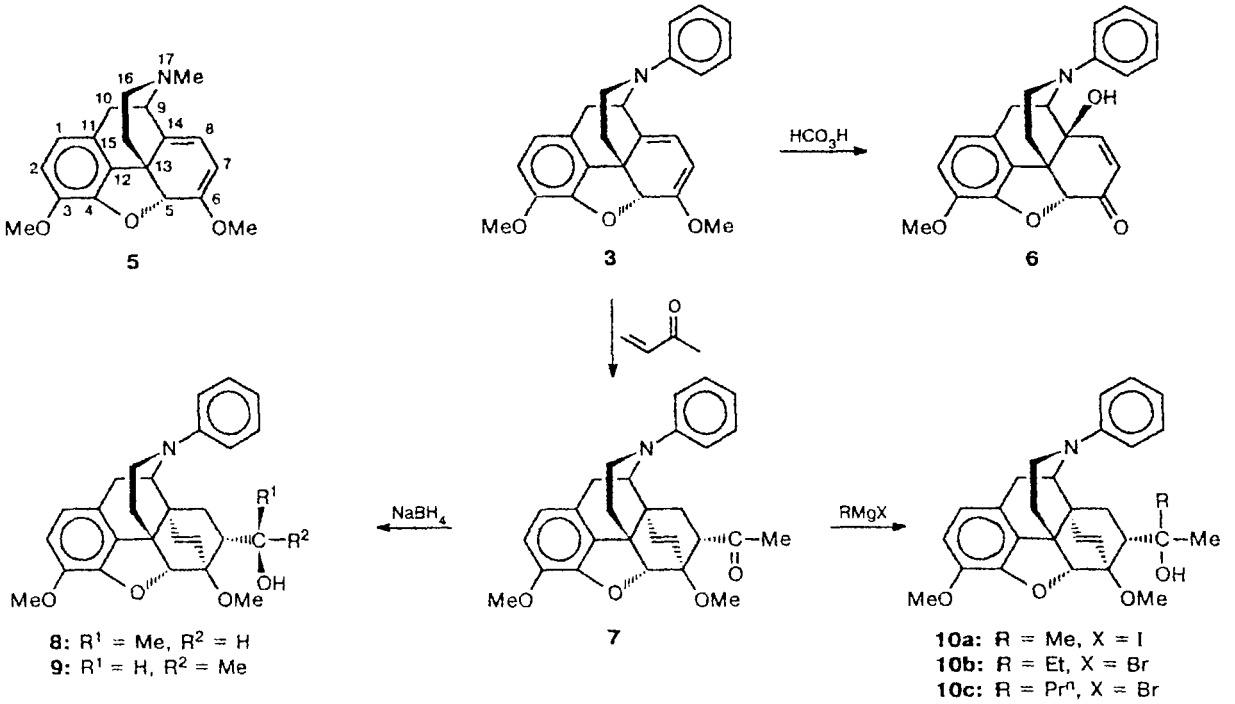


main reactions typical of compound **5** (oxidation, cycloaddition), and, hence, it could serve as the starting compound for the synthesis of other *N*-phenyl derivatives. This assumption has been confirmed experimentally (Scheme 2).

Compound **3** is readily oxidized by performic acid to give (14*S*)-14-hydroxy-17-phenyl-6-deoxy-17-norcodein-6-one (**6**) in a high yield. The oxidation of thebaine (**5**) gives a product with a similar structure.[6]

The reaction of but-3-en-2-one with *N*-phenylated derivative **3** proceeds similarly[7] to the cycloaddition of the same ketone to thebaine **5**. (6*R*,7*S*,14*R*)-7-(1-Oxoethyl)-17-phenyl-6,7,8,14-tetrahydro-6,14-etheno-17-northebaine (**7**) formed in this reaction can be easily

Scheme 2



converted into other *N*-phenyl-substituted alkaloids upon reactions involving the carbonyl group. In the present work, we studied the reduction of the carbonyl group in ketone **7** and the addition of Grignard reagents to it.

The reduction of **7** with $NaBH_4$ occurs nonselectively to give both possible diastereomeric alcohols **8** and **9**.

The reactions of **7** with MeMgI, EtMgBr, and Pr^nMgBr gave rise to the corresponding addition products **10a—c**. However, in the case of compounds **10b** and **10c**, which can exist as two diastereomers, only one of them was actually detected in the reaction mixture in each case, and the absolute configurations at the diastereogenic center could not be established.

Instead of the addition product, the reaction of ketone **7** with Bu^tMgCl gave the product of reduction of the carbonyl group in **7**, alcohol **9**, identical to one of the above-mentioned products of the reduction of **7** with $NaBH_4$; the isomeric alcohol was not detected in the reaction mixture. The absolute configurations at the diastereogenic center both in this product (**9**) and in the diastereomeric alcohol **8**, isolated after the reaction of **7** with $NaBH_4$, were established by X-ray diffraction analysis[8] and proved to be *S* and *R*, respectively. In turn, the structure of these products unambiguously indicates the structure of the starting ketone **7** (including the absolute configuration at the C(7) atom). Thus, the regio- and stereochemical outcomes of the cycloaddition reaction of but-3-en-2-one to compounds **3** (see above) and **5** [7] are identical.

Experimental

All reactions were carried out under dry argon. Dichloromethane was distilled over P_2O_5, and benzene and diethyl ether were distilled over sodium benzophenone ketyl.

The ^1H NMR spectra were recorded in $CDCl_3$ using a Bruker WP-200 SV spectrometer (operating at 200 MHz for ^1H); the chemical shifts are referred to internal tetramethylsilane. Mass spectra (EI, 70 eV) were run on an AEI-MS-30 mass spectrometer. IR spectra were measured on a UR-20 spectrometer in the form of pellets with KBr.

17-Phenyl-17-northebaine (3). Compound **1** (5.00 g, 0.017 mol) was added to a stirred mixture of Ph_3Bi (8.88 g, 0.020 mol) and $Cu(OAc)_2$ (3.05 g, 0.017 mol) in 150 mL of CH_2Cl_2. The mixture was refluxed with stirring for 130 h, cooled to ~20 °C, and filtered through a layer of Al_2O_3 (4 cm); the products were eluted with CH_2Cl_2. The filtrate was evaporated to dryness. The residue was recrystallized from MeOH to give 2.03 g (32.4%) of **3**, m.p. 177—178 °C. Found (%): C, 77.25; H, 6.22; N, 3.53. $C_{24}H_{23}NO_3$. Calculated (%): C, 77.19; H, 6.20; N, 3.75. ^1H NMR, δ: 3.61 (s, 3 H, OCH_3); 3.85 (s, 3 H, OCH_3); 5.35 (s, 1 H(5)); 5.08 and 5.68 (AB-system, 2 H, H(7) + H(8)); 6.55 and 6.66 (AB-system, 2 H, H(1) + H(2)); 6.81—7.35 (m, 5 H, C_6H_5). MS, *m/z* (I_{rel} (%)): 373 $[M]^+$ (100), 358 $[M - CH_3]^+$ (28), 242 (51), 104 (35), 77 $[C_6H_5]$ (31), 43 (46).

(6*R*,7*R*,14*S*)-7-[(2*S*)-2-Hydroxy-3,3-dimethylbut-2-yl]-17-phenyl-6,7,8,14-tetrahydro-6,14-ethano-17-northebaine (4). Compound **4** was prepared similarly to **3** from **2** (6.20 g, 0.014 mol), Ph_3Bi (7.64 g, 0.017 mol), and $Cu(OAc)_2$ (2.63 g, 0.014 mol). Yield 1.48 g (21%), m.p. 183—185 °C. Found (%): C, 76.54; H, 8.22; N, 2.57. $C_{32}H_{39}NO_4$. Calculated (%): C, 76.61; H, 7.84; N, 2.79. ^1H NMR, δ: 1.03 (s, 9 H, Bu^t); 1.44 (s, 3 H, CH_3); 3.63 (s, 3 H, OCH_3); 3.94 (s, 3 H, OCH_3); 4.53 (s, 1 H, H(5)); 6.56 and 6.75 (AB-system, 2 H, H(1) + H(2)); 6.88—7.32 (m, 5 H, C_6H_5). MS, *m/z* (I_{rel} (%)): 503 $[M]^+$ (34), 485 $[M - H_2O]^+$ (23), 470 $[M - H_2O - CH_3]^+$ (20), 446 $[M - C_4H_9]^+$ (43), 428 $[M - H_2O - C_4H_9]^+$ (36), 414 (100), 106 (68), 77 $[C_6H_5]$ (53), 57 $[C_4H_9]^+$ (53), 43 (73).

(14*S*)-14-Hydroxy-17-phenyl-6-deoxy-17-norcodein-6-one (6). Compound **3** (0.97 g, 2.60 mmol) was added with stirring to 10 mL of a mixture prepared from HCOOH (15 mL), water (13.6 mL), and H_2SO_4 (0.1 mL). The resulting solution was cooled to 15 °C, and 1.7 mL of a solution of performic acid, prepared from HCOOH (6.8 mL) and 30% aqueous H_2O_2 (3.3 mL), was added with stirring. The mixture was stirred at 15 °C for 30 min and poured into 200 mL of cold water. The resulting mixture was treated with stirring with 10% aqueous solution of ammonia until pH 9.0 was attained and extracted with $CHCl_3$ (3×50 mL). The combined extracts were dried with anhydrous Na_2SO_4, filtered, and evaporated to dryness. Chromatography on a SiO_2 column (elution with $CHCl_3$) followed by recrystallization from a benzene—hexane (2 : 1) mixture gave 0.46 g (49%) of **6**, m.p. 187.5—188.5 °C. Found (%): C, 73.20; H, 5.89; N, 3.40. $C_{23}H_{21}NO_4$. Calculated (%): C, 73.58; H, 5.64; N, 3.73. IR, ν/cm^{-1}: 3430 (OH); 1690 (C=O). ^1H NMR, δ: 3.92 (s, 3 H, OCH_3); 4.93 (s, 1 H, H(5)); 6.27 and 6.69 (AB-system, 2 H, H(7) + H(8)); 6.58 and 6.69 (AB-system, 2 H, H(1) + H(2)); 6.96—7.42 (m, 5 H, C_6H_5). MS, *m/z* (I_{rel} (%)): 375 $[M]^+$ (28), 374 $[M - 1]^+$ (9), 373 $[M - 2]^+$ (45), 276 (15), 266 (10), 169 (9), 149 (89), 121 (31), 119 (55), 105 $[CH_2{=}NC_6H_5]^+$ (45), 104 (100), 103 (64), 93 (91), 77 $[C_6H_5]$ (92).

(6*R*,7*S*,14*R*)-7-(1-Oxoethyl)-17-phenyl-6,7,8,14-tetrahydro-6,14-etheno-17-northebaine (7). Compound **3** (1.26 g, 3.37 mmol) was heated in 30 mL of but-3-en-2-one at 90 °C for 30 min, and the mixture was concentrated to dryness. The residue was recrystallized from MeOH to give 1.28 g (86%) of **7**, m.p. 128—130 °C. Found (%): C, 75.92; H, 6.51; N, 3.00. $C_{28}H_{29}NO_4$. Calculated (%): C, 75.82; H, 6.59; N, 3.16. ^1H NMR, δ: 2.10 (s, 3 H, $COCH_3$); 3.57 (s, 3 H, OCH_3); 3.77 (s, 3 H, OCH_3); 4.60 (s, 1 H, H(5)); 5.57 and 5.93 (AB-system, 2 H, H(18) + H(19)); 6.43 and 6.68 (AB-system, 2 H, H(1) + H(2)); 6.80—7.27 (m, 5 H, C_6H_5).

(6*R*,7*R*,14*R*)-7-[(1*R*)-1-Hydroxyethyl]-17-phenyl-6,7,8,14-tetrahydro-6,14-etheno-17-northebaine (8) and (6*R*,7*R*,14*R*)-7-[(1*S*)-1-hydroxyethyl]-17-phenyl-6,7,8,14-tetrahydro-6,14-etheno-17-northebaine (9). Compound **7** (1.00 g, 2.25 mmol) was added to a solution of $NaBH_4$ (0.10 g, 2.70 mmol) in 70 mL of MeOH. The mixture was refluxed for 1 h, concentrated to 20 mL, and poured into 100 mL of water. The reaction products were extracted with $CHCl_3$ (3×30 mL), and the combined extracts were concentrated to dryness. The reaction products were separated by preparative TLC on a SiO_2 plate (elution with $CHCl_3$) and recrystallized from MeOH to give 0.32 g (32%) of **8** and 0.35 g (33%) of **9** · CH_3OH.

Compound 8, m.p. 123—125 °C. Found (%): C, 75.54; H, 6.97; N, 2.73. $C_{28}H_{31}NO_4$. Calculated (%): C, 75.48; H, 7.01; N, 3.14. ^1H NMR, δ: 1.09 (d, 3 H, CH_3); 3.77 (s, 3 H, OCH_3); 3.83 (s, 3 H, OCH_3); 4.63 (s, 1 H, H(5)); 5.57 and 6.00 (AB-system, 2 H, H(18) + H(19)); 6.49 and 6.63 (AB-system, 2 H, H(1) + H(2)); 6.84—7.24 (m, 5 H, C_6H_5).

Compound 9 · CH_3OH, m.p. 94.5—96 °C. Found (%): C, 72.92; H, 7.23; N, 2.38. $C_{29}H_{35}NO_5$. Calculated (%):

C, 72.93; H, 7.39; N, 2.93. ^{1}H NMR ($CDCl_3$), δ: 1.07 (d, 3 H, CH_3); 3.66 (s, 3 H, OCH_3); 3.81 (s, 3 H, OCH_3); 4.63 (s, 1 H, H(5)); 5.49 and 5.88 (AB-system, 2 H, H(18) + H(19)); 6.58 and 6.61 (AB-system, 2 H, H(1) + H(2)); 6.80—7.36 (m, 5 H, C_6H_5).

Reaction of compound 7 with Bu^{t}MgCl. A solution of 7 (0.48 g, 1.08 mmol) in 30 mL of benzene was added dropwise with stirring to a solution of Bu^{t}MgCl prepared from Mg (0.05 g, 2.16 mmol) and Bu^{t}Cl (0.20 g, 2.16 mmol). The mixture was refluxed with stirring for 1 h and cooled to ~20 °C, and 70 mL of a saturated aqueous solution of NH_4Cl was slowly added. The organic layer was separated. The aqueous layer was extracted with $CHCl_3$ (3×30 mL). The organic layer and the extracts were combined, dried with anhydrous Na_2SO_4, and concentrated to dryness. The residue was recrystallized from MeOH to give 0.14 g (29%) of **9** · CH_3OH.

(6*R*,7*R*,14*R*)-7-(2-Hydroxyprop-2-yl)-17-phenyl-6,7,8,14-tetrahydro-6,14-etheno-17-northebaine (10a). A solution of 7 (0.70 g, 1.58 mmol) in 30 mL of benzene was added dropwise with stirring to a solution of MeMgI, prepared from Mg (0.12 g, 5.00 mmol) and MeI (1.00 g, 7.00 mmol) in 80 mL of ether. The mixture was stirred for 30 min, and 100 mL of a saturated aqueous solution of NH_4Cl was slowly added; the resulting **10a** was isolated as described in the previous procedure for **9** · CH_3OH to give 0.54 g (74%) of **10a**, m.p. 221—222.5 °C. Found (%): C, 75.73; H, 7.07; N, 2.94. $C_{29}H_{33}NO_4$. Calculated (%): C, 75.79; H, 7.24; N, 3.05. ^{1}H NMR, δ: 1.03 (s, 3 H, CH_3); 1.09 (s, 3 H, CH_3); 3.79 (s, 3 H, OCH_3); 3.83 (s, 3 H, OCH_3); 4.62 (s, 1 H, H(5)); 5.48 and 6.04 (AB-system, 2 H, H(18) + H(19)); 6.46 and 6.63 (AB-system, 2 H, H(1) + H(2)); 6.83—7.35 (m, 5 H, C_6H_5).

(6*R*,7*R*,14*R*)-7-(2-Hydroxybut-2-yl)-17-phenyl-6,7,8,14-tetrahydro-6,14-etheno-17-northebaine (10b). A solution of 7 (0.50 g, 1.12 mmol) in 30 mL of benzene was added dropwise with stirring to a solution of EtMgBr, prepared from Mg (0.11 g, 4.60 mmol) and EtBr (0.50 g, 4.60 mmol) in 80 mL of ether. The mixture was stirred at ~20 °C for 30 min, and 100 mL of a saturated aqueous solution of NH_4Cl was added dropwise. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2×50 mL). The organic layer and the extracts were combined and concentrated *in vacuo*, and the residue was recrystallized from MeOH to give 0.35 g (65%) of **10b**, m.p. 212—214.5 °C. Found (%): C, 75.70; H, 7.51; N, 2.50. $C_{30}H_{35}NO_4$. Calculated (%): C, 76.08; H, 7.45; N, 2.96. ^{1}H NMR (CD_2Cl_2), δ: 0.95 (s, 3 H, CH_3); 3.71 (s, 3 H, OCH_3); 3.77 (s, 3 H, OCH_3); 4.54 (s, 1 H, H(5)); 5.45 and 6.00 (AB-system, 2 H, H(18) + H(19)); 6.42 and 6.60 (AB-system, 2 H, H(1) + H(2)); 6.77—7.30 (m, 5 H, C_6H_5).

(6*R*,7*R*,14*R*)-7-(2-Hydroxypent-2-yl)-17-phenyl-6,7,8,14-tetrahydro-6,14-etheno-17-northebaine (10c). A solution of 7 (0.97 g, 2.17 mmol) in 50 mL of benzene was added dropwise with stirring to a solution of PrMgBr prepared from Mg (0.19 g, 7.80 mmol) and Pr^{n}Br (0.96 g, 7.80 mmol) in 150 mL of ether. The mixture was stirred at ~20 °C for 3 h, and 150 mL of a saturated aqueous solution of NH_4Cl was added dropwise. The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (2×70 mL). The organic layer and the extracts were combined and concentrated *in vacuo*, and the residue was chromatographed (PTLC) on a SiO_2 plate (elution with $CHCl_3$). The product was recrystallized from MeOH to give 0.43 g (34%) of **10c**, m.p. 178—179 °C. Found (%): C, 76.08; H, 7.75; N, 2.80. $C_{31}H_{37}NO_4$. Calculated (%): C, 76.35; H, 7.65; N, 2.88. ^{1}H NMR, δ: 0.96 (s, 3 H, CH_3); 3.74 (s, 3 H, OCH_3); 3.80 (s, 3 H, OCH_3); 4.58 (s, 1 H, H(5)); 5.43 and 6.02 (AB-system, 2 H, H(18)+H(19)); 6.43 and 6.58 (AB-system, 2 H, H(1) + H(2)); 6.83—7.33 (m, 5 H, C_6H_5).

This work was financially supported by the Russian Foundation for Basic Research (Project No. 96-03-33376) and the INTAS (joint project of the INTAS and the RFBR No. IR-97-12060).

References

1. G. R. Lenz, S. M. Evans, D. E. Walters, and A. J. Hopfinger, in *Opiates*, publs. Harcourt, Brace, Jovanovich, Acad. Press, Inc., Orlando—London, 1986, a) p. 72; b) p. 102.
2. V. N. Kalinin, I. V. Bakhanova, V. V. Kobak, and S. K. Moiseev, *Izv. Akad. Nauk, Ser. Khim.*, 1997, 879 [*Russ. Chem. Bull.*, 1997, **46**, 845 (Engl. Transl.)].
3. R. A. Abramovitch, D. H. R. Burton, and J. P. Finet, *Tetrahedron*, 1988, **44**, 3039; T. Arnauld, D. H. R. Burton, and E. Doris, *Tetrahedron*, 1997, **53**, 4137 and references therein.
4. Neth. Appl. 6515815; *Chem Abstr.*, 1966, **65**, 15441d.
5. Brit. Pat. 1136214; *Chem Abstr.*, 1966, **70**, 78218s.
6. F. M. Hauser, Tek-Kuei Chen, and F. I. Carroll, *J. Med. Chem.*, 1974, **17**, 1117.
7. K. W. Bentley and D. G. Hardy, *J. Am. Chem. Soc.*, 1967, **89**, 3267.
8. I. V. Bakhanova, V. N. Nesterov, S. K. Moiseev, H. Shmidhammer, and V. N. Kalinin, *Izv. Akad. Nauk, Ser. Khim.*, 1998, 2245 [*Russ. Chem. Bull.*, 1998, **47**, 2177 (Engl. Transl.)].

Received January 5, 1999