Monatshefte für Chemie 137, 1203–1210 (2006)
DOI 10.1007/s00706-006-0516-y

**Monatshefte für Chemie**
**Chemical Monthly**
Printed in Austria

# A Convenient Way to Methylated 2-Imidazolines. Syntheses of Fluorene and Triazine Cyclic Diamidines

**Jaroslaw Spychala***

Department of Chemistry, Adam Mickiewicz University, Poznan, Poland

Received December 7, 2005; accepted (revised) January 16, 2006
Published online September 8, 2006 

**Summary.** One *N*-methyl- and 4-substituted 2-imidazolines are described. Fluorene bisimidazolines were obtained in good yield (64–92%), starting from 2,7-dicyanofluorene and ammonium sulfide. In a two-step procedure the crude bisthioamide was reacted with excess diaminoalkane-ethanol (1:1 mixture) in an oil bath. This new procedure is superior over standard methods. For the sake of comparison, a new triazine bisimidazoline was prepared by direct conversion of the appropriate bisnitrile. Preliminary in vitro studies have shown an interesting anticancer activity of this compound (NSC 710607) against diverse human cancer types, including colon, CNS, melanoma, breast, non-small cell lung, and ovarian.

**Keywords.** Diamidines; Fluorenes; 2-Imidazolines; Triazines; Uracils.

## Introduction

Cyclic amidines were found to exhibit a vast array of biological activities as antiviral, cytotoxic, antibacterial, antiprotozoal, antitrypanosomal, antiproteolytic, antigiardial, antifungal, antiarrhythmic, antihistaminic, sympathomimetic, and adrenergic [1]. Numerous molecules have proven to be useful nasal decongestants, circulatory stimulants, and enzyme inhibitors and have also found use in industry as emulsifiers, textile aids, flotation agents, asphalt additives, and corrosion resistors. The occurrence of antibiotic substances was reported [2]. Biochemical and biophysical studies on their interactions with nucleic acids have been conducted [3]. Selected members have been evaluated for their *in vitro* and *in vivo* inhibitory properties to establish their potential benefit in the treatment of cancer in humans [4]. This paper is concerned with a practical synthesis of some methylated 2-imidazolines.

* E-mail: jjspycha@amu.edu.pl

## Results and Discussion

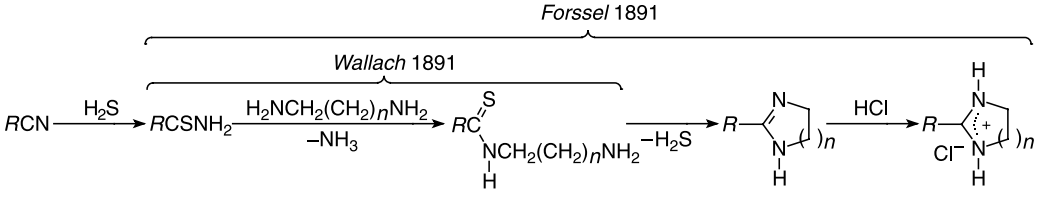
### *Synthesis of N-alkyl-2-imidazolines*

2-Substituted 1-alkyl-2-imidazolines are not too readily available in comparison with unsubstituted appropriate 1*H*-derivatives [5–8]. One procedure involves the *Pinner* synthesis [5]. Other methods include the reaction of nitriles [6] or acids (esters) [7] with N-substituted ethylenediamines and the alkylation reaction of 2-imidazoline derivatives [8]. Synthesis of cyclic amidines has involved a secondary thioamide intermediate (Scheme 1) [9–11]. The outcome of these studies prompted me to explore the possibility of using *N*-methylethylenediamine for the preparation of *N*-methyl-2-imidazoline derivatives, as a support for the mechanism presented.

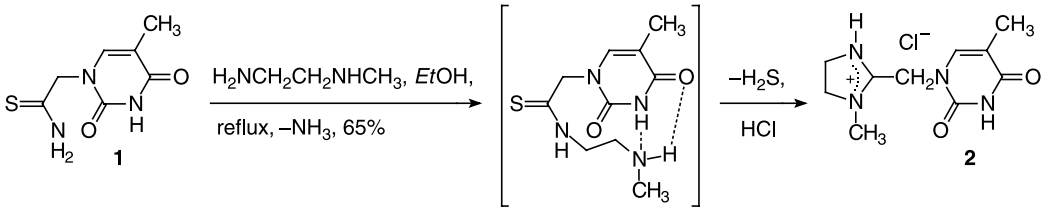
The formation of *N*-methylimidazoline **2** from primary thioamide **1** and *N*-methylethylenediamine confirms different reactivities of ethylenediamine derivatives (Scheme 2). The N-substituent of the diaminoalkane causes a relatively stronger intramolecular cooperative hydrogen bonding interaction than the $NH_2$ group. As shown previously, the reactivities of substrates can be predicted on the basis of the NMR spectra of secondary amides, if appropriate thioamides are difficult to obtain. In this connection, attention should be drawn to the work about the mechanism of direct reactions of nitriles to secondary (thio)amides or cyclic amidines [10, 12].

### *Synthesis of Fluorene Bisimidazolines by a Two-Stage Procedure*

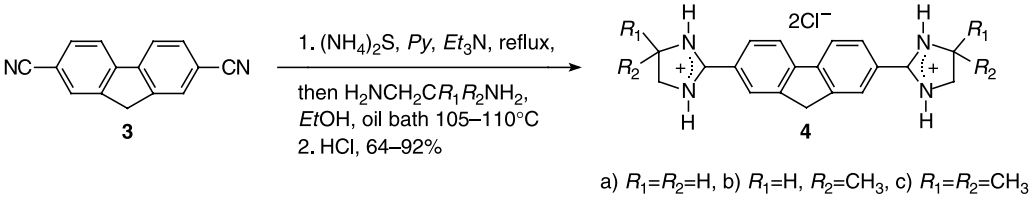
The classic access to cyclic amidines lies in the use of thioamides [13]. The application of an ammonium sulfide solution for a transformation of 2,7-dicyanofluorene (**3**) into bisimidazoline **4** in two steps without purification of the intermediate is reported here (Scheme 3). Bisnitrile **3** was reacted with the 20–22% $(NH_4)_2S$ in water-pyridine-triethylamine reagent (some cyano groups remained unaffected as determined by IR spectroscopy). When the crude thioamide in a



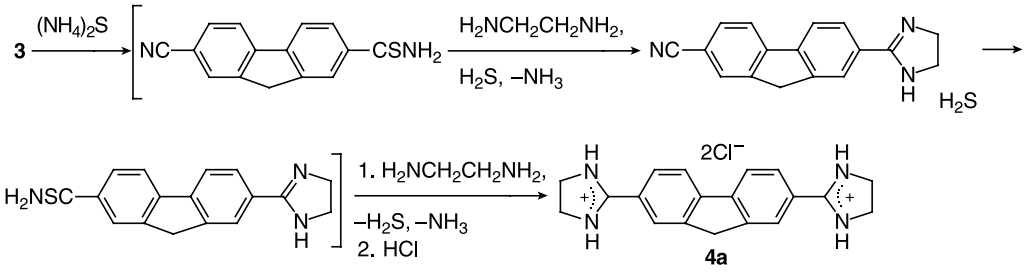

**Scheme 1**




**Scheme 2**




**Scheme 3**



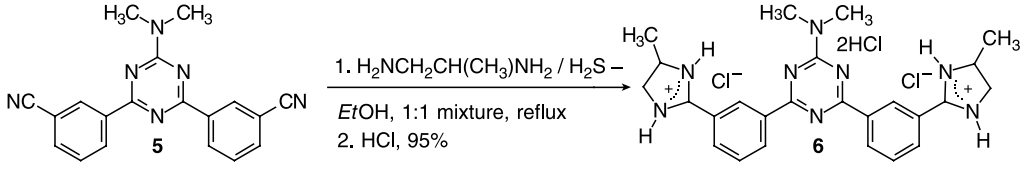

**Scheme 4**

diaminoalkane-ethanol mixture, an excess of which served as solvent, was heated in an oil bath only diamidine **4** was formed.

The reaction proceeds *via* a secondary thioamide intermediate (Scheme 4). The intramolecular cyclization reaction [14] occurs with the evolution of hydrogen sulfide. The latter is necessary for the conversion of an unreacted cyano group into the thiocarbamoyl group (loss of $H_2S$ and base catalyzed re-addition). It was possible to obtain the pure product without isolating unreacted cyanides. Hence, the new procedure is of technological significance and represents a good alternative to the commonly used methods.

*Synthesis of a Triazine Bisimidazoline by a One-Stage Procedure*

The influence of the reaction conditions has been examined. Among other methodologies reported in the literature for cyclic amidines is the direct reaction of nitriles with excess diaminoalkane-hydrogen sulfide reagent [9]. This procedure gives satisfactory results for triazine diamidine **6** (Scheme 5), but its value is limited for **4**, due to considerable decomposition during refluxing (the mixture had a greenish-blue fluorescence). The synthesis of tetrahydrochloride salt **6** was achieved directly from dinitrile **5** by adopting the method for the preparation of 4,6-bis[4-(4,5-dihydro-4-methyl-1*H*-imidazol-2-yl)phenyl]-2-dimethylamino-1,3,5-triazine dihydrochloride (**7**) [9].




**Scheme 5**

*Anticancer Activity for the Triazine Bisimidazolines*

Compound **6** (NSC 710607) was screened for anticancer inhibitory activity by the National Cancer Institute's *in vitro* testing against the full panel of 60 human tumor cell lines and was shown to have inhibitory properties especially against different colon (COLO 205, HCC-2998, HCT-116), central nervous system (SF-539, SNB-75, U251), melanoma (LOX IMVI, SK-MEL-2, SK-MEL-5, UACC-62), breast (MCF7, NCI/ADR-RES, MDA-MB-231/ATCC, MDA-MB-435, MDA-N), non-small cell lung (NCI-H522), and ovarian (OVCAR-4) cancer types (Fig. 1). Also isomer **7** (NSC 710608) exhibited reasonable activity (log $GI_{50} < -4.00$; $GI_{50}$ molar concentration of the compound that inhibits 50% net cell growth) against most of cancer cell lines but only **6** has received attention of the NCI's Biological Evaluation Committee for Cancer Drugs (Frederick, MD) for further testing in an *in vivo* anticancer hollow fiber assay and related acute toxicity studies.

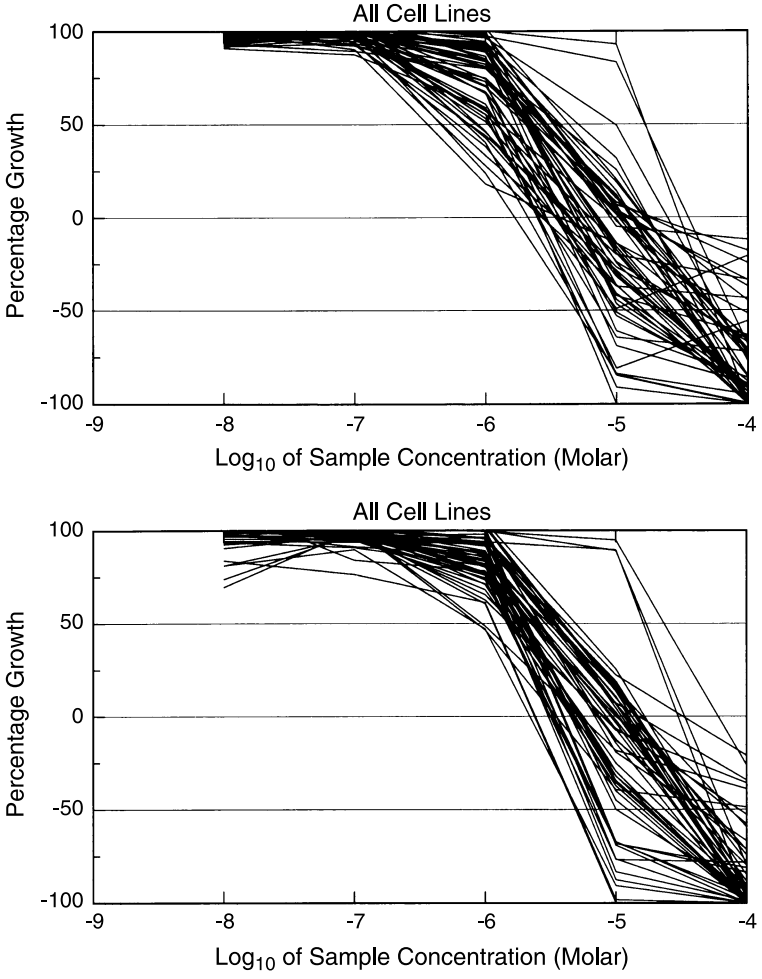



**Fig. 1.** Overview of the results of the *in vitro* antitumor screening for active compounds **6** (top) and **7** (bottom); from the data it can be seen that the positions of two amidino groups did not greatly alter anticancer activity

In conclusion, *N*-methylimidazolines can be prepared from thioamides and *N*-methylethylenediamine. A practical procedure has been worked out for converting 2,7-dicyanofluorene to other methyl-substituted bisimidazolines by a two-stage process. The direct reaction gives satisfactory results for triazine diamidines, but its value is limited when other functional groups in the molecule may be affected by the reagent. The new procedure overcomes the limitations of the latter method. The *in vitro* biological data prove usefulness of the cationic system in the design of new active anticancer agents (NSC 710607 and NSC 710608). The shape of molecules (radius of curvature) did not change the affinity of the selected compounds for anticancer activity.

## Experimental

Melting points are uncorrected and were determined by using a Boetius melting-point apparatus. NMR spectra were recorded on a Varian 300 Gemini spectrometer ($^1$H 300 MHz and $^{13}$C 75 MHz) in DMSO-$d_6$ solutions with *TMS* as a standard (unless otherwise indicated), and IR spectra were recorded on a Bruker FT-IR spectrometer (KBr). High resolution mass spectra were obtained using an AMD 402 or 602 mass spectrometer in the EI or FAB mode, respectively. *DSS* = sodium 2,2-dimethyl-2-silapentane-5-sulfonate. Thin-layer chromatography (TLC) was performed with Merck silica gel 60$F_{254}$ plates (0.25 mm thickness) in the following developing solvent systems (*v*/*v*): 18:1 (A), $CHCl_3$–$CH_3OH$ and 44:8:1 (B), 11:4:1 (C), 7:5:2 (D), $CHCl_3$–$CH_3OH$–$NH_4OH$. The amine zones were made visible by spraying with an ethanolic solution of ninhydrin (200 mg in 100 cm$^3$) and heating the plates. All final samples were dried first in an oven at 120°C and then stored in a vacuum desiccator over phosphorus pentoxide. Diaminoalkanes were purified by distillation from sodium. Ethylenediamine, (±)-1,2-diaminopropane, 1,2-diamino-2-methylpropane, 2,7-dibromofluorene, and copper(I) cyanide were available from Aldrich. 33% Dimethylamine in absolute ethanol was purchased from Merck and 20–22% ammonium sulfide solution in water from Fluka.

*2-(1-Thyminyl)methyl-4,5-dihydro-1-methylimidazole hydrochloride* (**2**, $C_{10}H_{14}N_4O_2$)

A mixture of 0.6984 g **1** (0.0042 mol) [11] and 0.3135 g *N*-methylethylenediamine (0.0042 mol) in 10 cm$^3$ absolute ethanol was heated under reflux with stirring for 18 h. The reagents and apparatus used in this experiment must be strictly dry, or a large amount of a secondary amide will be formed. The mixture was treated with 10 cm$^3$ isopropanol, refrigerated, filtered, and the free base was acidified with 1 *N* HCl. Upon recrystallization from methanol the pure product was obtained. The product was detected by TLC in a mixture of solvent systems C and D. Yield 65%; mp > 300°C (242–245°C for the free base); $^1$H NMR: $\delta$(free base) = 1.74 (s, 3H, C*H*$_3$), 2.75 (s, 3H, NC*H*$_3$), 3.22 (t, 2H, $J$ = 9.5 Hz, C*H*$_2$), 3.45 (t, 2H, $J$ = 9.2 Hz, C*H*$_2$), 4.45 (s, 2H, C*H*$_2$), 7.39 (s, 1H, C6*H*), 10.92 (br s, 1H, N3*H*) ppm; $^{13}$C NMR: $\delta$ (free base) = 12.0, 33.2, 43.6, 51.9, 53.5, 108.0, 142.0, 150.8, 162.8, 164.4 ppm; $^1$H NMR: $\delta$ = 1.77 (s, 3H, C*H*$_3$), 3.09 (s, 3H, NC*H*$_3$), 3.77 (dt, 2H, $J$ = 9.7, 2.8 Hz, C*H*$_2$), 3.92 (dt, 2H, $J$ = 10.3, 2.9 Hz, C*H*$_2$), 4.94 (s, 2H, C*H*$_2$), 7.57 (s, 1H, C6*H*), 10.22 (br s, 1H, N*H*), 11.51 (s, 1H, N3*H*) ppm; $^{13}$C NMR: $\delta$ = 12.1, 32.6, 42.7, 52.0, 110.0, 140.4, 151.0, 164.5, 165.4 ppm; $^1$H NMR ($D_2O$, *DSS*): $\delta$ = 1.91 (d, 3H, $J$ = 1.1 Hz, C*H*$_3$), 3.17 (s, 3H, NC*H*$_3$), 3.88 (dt, 2H, $J$ = 10.8, 3.0 Hz, C*H*$_2$), 4.04 (dt, 2H, $J$ = 10.4, 3.0 Hz, C*H*$_2$), 4.84 (s, 2H, C*H*$_2$), 7.48 (d, 1H, $J$ = 1.4 Hz, C6*H*) ppm; $^{13}$C NMR ($D_2O$, *DSS*): $\delta$ = 14.2, 35.1, 45.7, 46.4, 55.1, 115.0, 144.1, 154.7, 167.1, 169.3 ppm; LRMS (EI): *m*/*z* (%) = 222 (100), 207 (3), 179 (23), 151 (17), 139 (14); HRMS (EI): $M^{+\cdot}$ found 222.1108 $C_{10}H_{14}N_4O_2$ requires 222.1117.

*2,7-Dicyanofluorene* (**3**, $C_{15}H_8N_2$)

A mixture of 24.5 g 2,7-dibromofluorene (0.0756 mol), 15 g copper(I) cyanide (0.1675 mol), and 150 cm$^3$ quinoline was refluxed with stirring for 3 h. The resulting mixture was poured into excess

aqueous solution of iron(III) chloride in dilute hydrochloric acid to decompose the complex. The precipitate was collected, washed with water, and extracted in a *Soxhlet* apparatus with chloroform. Evaporation of the solvent to dryness, followed by crystallization of the residue from 2-methoxyethanol gave chromatographically pure needles (solvent system A or anhydrous $CHCl_3$).

Yield 51%; mp 287–289°C (Ref. [15a] 285°C, Ref. [15b] 264°C, Ref. [15c] 269–270°C); IR: $\bar{\nu} = 2228$, 1390, 1295, 1105, 1016, 920, 845, 590, 534 $cm^{-1}$; $^1H$ NMR: $\delta = 4.10$ (s, 2H, $CH_2$), 7.88 (d, 2H, $J = 7.8$ Hz), 8.09 (s, 2H), 8.22 (d, 2H, $J = 7.8$ Hz) ppm; $^1H$ NMR ($CDCl_3$, *TMS*): $\delta = 4.03$ (s, 2H, $CH_2$), 7.73 (dd, 2H, $J = 8.3$, 1.0 Hz), 7.87 (s, 2H), 7.91 (d, 2H, $J = 8.3$ Hz) ppm; $^{13}C$ NMR ($CDCl_3$, *TMS*): $\delta = 36.8$, 111.9, 118.9, 121.6, 129.0, 131.6, 144.3, 144.2 ppm; LRMS (EI): $m/z$ (%) = 216 (100), 188 (25), 164 (6), 140 (3), 108 (9); HRMS (EI) $M^{+\cdot}$ found 216.0703 $C_{15}H_8N_2$ requires 216.0687.

*General Procedure for the Synthesis of Compounds* ***4***

A mixture of 5.35 g 2,7-dicyanofluorene (**3**, 0.025 mol), 20 $cm^3$ 20–22% ammonium sulfide solution in water, 50 $cm^3$ pyridine, and 10 $cm^3$ triethylamine was heated under reflux with stirring for 1 h. After cooling, water was added and the solid was filtered off and dried in a vacuum desiccator at 100°C over $P_2O_5$ (yield 6.08 g). TLC (system A) showed an amount of the unaltered substrate. The infrared spectrum contained the characteristic C≡N stretching band at 2228 $cm^{-1}$. The crude thioamide (1 g), 5 $cm^3$ appropriate diamine and 5 $cm^3$ anhydrous ethanol were heated in an oil bath at 105–110°C for 18 h. After cooling, 25 $cm^3$ water were added and the product was collected by filtration, washed successively with water and dried. The free base was converted into the dihydrochloride salt with 1 *N* hydrochloric acid and tetrahydrofuran (systems B and C). The dihydrochlorides **4b** and **4c** were additionally crystallized from ethanol-tetrahydrofuran and isopropanol-tetrahydrofuran, respectively. Yields were calculated on the basis of starting bisnitrile **3**.

*2,7-Bis(4,5-dihydro-1H-imidazol-2-yl)fluorene dihydrochloride* (**4a**, $C_{19}H_{18}N_4$)

Yield 92%; mp > 300°C; IR: $\bar{\nu} = 3399$, 3107, 2972, 1617, 1595, 1560, 1473, 1421, 1406, 1364 $cm^{-1}$; $^1H$ NMR ($D_2O$, *DSS*): $\delta = 3.58$ (s, 2H), 3.97 (s, 8H), 7.42 (d, 2H, $J = 8.0$ Hz), 7.56 (s, 2H), 7.60 (d, 2H, $J = 8.0$ Hz) ppm; $^{13}C$ NMR ($D_2O$, *DSS*): $\delta = 38.9$, 47.0, 122.4, 124.2, 126.6, 129.1, 147.0, 166.7 ppm; LRMS (EI): $m/z$ (%) = 302 (100), 273 (84), 244 (25), 204 (11), 190 (23); HRMS (EI): $M^{+\cdot}$ found 302.1490 $C_{19}H_{18}N_4$ requires 302.1531.

*(±)-2,7-Bis(4,5-dihydro-4-methyl-1H-imidazol-2-yl)fluorene dihydrochloride* (**4b**, $C_{21}H_{22}N_4$)

Yield 64%; mp > 300°C; IR: $\bar{\nu} = 3434$, 3093, 2969, 1618, 1599, 1554, 1474, 1401, 1374, 1334 $cm^{-1}$; $^1H$ NMR ($D_2O$, *DSS*): $\delta = 1.51$ (d, 6H, $J = 6.3$ Hz), 3.72 (dd, 2H, $J = 11.3$, 8.2 Hz), 3.96 (s, 2H), 4.22 (t, 2H, $J = 11.3$ Hz), 4.57 (m, 2H), 7.72 (d, 2H, $J = 7.9$ Hz), 7.90 (s, 2H), 7.97 (d, 2H, $J = 8.1$ Hz) ppm; $^{13}C$ NMR ($D_2O$, *DSS*): $\delta = 22.7$, 39.0, 53.8, 56.1, 122.9, 124.3, 126.7, 129.2, 147.2, 147.3, 166.1 ppm; LRMS (EI): $m/z$ (%) = 330 (86), 316 (100), 301 (18), 288 (73), 258 (28); HRMS (EI): $M^{+\cdot}$ found 330.1827 $C_{21}H_{22}N_4$ requires 330.1845 $[M–CH_3]^+$ found 315.1602 $C_{20}H_{19}N_4$ requires 315.1610.

*2,7-Bis(4,5-dihydro-4,4-dimethyl-1H-imidazol-2-yl)fluorene dihydrochloride* (**4c**, $C_{23}H_{26}N_4$)

Yield 74%; mp > 300°C; IR: $\bar{\nu} = 3516$, 3444, 3048, 2930, 1615, 1599, 1550, 1472, 1421, 1356 $cm^{-1}$; $^1H$ NMR ($D_2O$, *DSS*): $\delta = 1.62$ (s, 12H), 3.93 (s, 4H), 4.03 (s, 2H), 7.78 (d, 2H, $J = 7.5$ Hz), 7.96 (s, 2H), 8.03 (d, 2H, $J = 8.2$ Hz) ppm; $^{13}C$ NMR ($D_2O$, *DSS*): $\delta = 29.7$, 39.1, 59.5, 64.4, 123.6, 124.4, 126.9, 129.4, 147.5, 147.6, 165.4 ppm; LRMS (EI): $m/z$ (%) = 358 (27), 343 (100), 301 (11), 272 (18), 244 (3); HRMS (EI): $M^{+\cdot}$ found 358.2129 $C_{23}H_{26}N_4$ requires 358.2158 $[M–CH_3]^+$ found 343.1934 $C_{22}H_{23}N_4$ requires 343.1923.

*(±)-4,6-Bis[3-(4,5-dihydro-4-methyl-1H-imidazol-2-yl)phenyl]-2-dimethylamino-1,3,5-triazine tetrahydrochloride* (**6**, $C_{25}H_{28}N_8 \cdot 4HCl$)

A 1:1 mixture of (±)-1,2-diaminopropane-absolute ethanol (10 $cm^3$) was saturated with hydrogen sulfide and 0.9300 g 4,6-bis(3-cyanophenyl)-2-dimethylamino-1,3,5-triazine (**5**, 0.0029 mol) [16] were

added. The mixture was heated under reflux for 18 h. By this time complete solution was achieved. The residue was left overnight in the refrigerator. Crystallization was slow. The free base was precipitated with water and then recrystallized from methanol (20 $cm^3$). The product was converted to its respective tetrahydrochloride salt with excess 1 *N* HCl, evaporated to dryness, dissolved in methanol and precipitated with diethyl ether. On cooling the mixture in the refrigerator, chromatographically homogeneous crystals separated (according to chromatography in the solvent system D), which were collected by filtration, and washed with isopropanol. Yield 55% (evaporation of the reaction mixture to dryness greatly increased the yield to 95%); mp > 300°C; IR: $\bar{\nu}$ = 3407, 3058, 2933, 1618, 1568, 1549, 1509, 1440, 1414, 1378 $cm^{-1}$; $^1$H NMR: $\delta$ (free base) = 1.23 (d, 6H, $J$ = 6.3 Hz, 2C$H_3$), 3.29 (dd, 2H, $J$ = 11.8, 7.7 Hz), 3.38 (s, 6H, C$H_3$NC$H_3$), 3.86 (t, 2H, $J$ = 11.0 Hz), 4.10 (m, 2H), 4.30 (br s, 2H, N*H*), 7.67 (t, 2H, $J$ = 7.8 Hz), 8.07 (d, 2H, $J$ = 8.0 Hz), 8.67 (d, 2H, $J$ = 7.7 Hz), 8.97 (d, 2H, $J$ = 1.4 Hz) ppm; $^1$H NMR: $\delta$ = 1.44 (d, 6H, $J$ = 6.4 Hz, 2C$H_3$CH), 3.40 (s, 6H, 2C$H_3$), 3.64 (dd, 2H, $J$ = 11.1, 8.1 Hz, 2C*H*H), 4.19 (t, 2H, $J$ = 11.3 Hz, 2CH*H*), 4.51–4.60 (m, 2H, 2$CH_3$C*H*), 7.88 (t, 2H, $J$ = 7.9 Hz), 8.31 (d, 2H, $J$ = 7.9 Hz), 8.46 (br s, 2H, triazine 2N*H*), 8.94 (d, 2H, $J$ = 7.9 Hz), 9.34 (d, 2H, $J$ = 1.7 Hz), 11.10 (s, 2H, imidazoline NH), 11.35 (s, 2H, imidazoline NH) ppm; $^{13}$C NMR: $\delta$ = 20.5, 36.2, 51.0, 53.1, 122.7, 128.7, 129.6, 132.2, 134.0, 137.1, 162.8, 164.7, 168.7 ppm; HRMS (EI): $M^{+\cdot}$ found 440.2451 $C_{25}H_{28}N_8$ requires 440.2437 $[M–CH_3]^+$ found 425.2214 $C_{24}H_{25}N_8$ requires 425.2202; $C_{25}H_{28}N_8 \cdot 4HCl \cdot 4H_2O$ (658.44): found C 45.53 H 6.13 N 17.18, calcd C 45.60 H 6.12 N 17.02 (Vario EL III elemental analyzer).

*(±)-4,6-Bis[4-(4,5-dihydro-4-methyl-1H-imidazol-2-yl)phenyl]-2-dimethylamino-1,3,5-triazine dihydrochloride* (**7**, $C_{25}H_{28}N_8 \cdot 2HCl$)
The free base was converted to its dihydrochloride salt with two equivalents of 1 *N* HCl. $^1$H NMR: $\delta$ = 1.42 (d, 6H, $J$ = 6.2 Hz, C$H_3$CH), 3.34 (s, 6H, C$H_3$), 3.63 (dd, 2H, $J$ = 11.3, 8.1 Hz, C*H*H), 4.18 (t, 2H, $J$ = 11.3 Hz, CH*H*), 4.48–4.61 (m, 2H, $CH_3$C*H*), 8.28 (d, 4H, $J$ = 8.7 Hz), 8.73 (d, 4H, $J$ = 8.5 Hz), 11.17 (br s, 4H, N*H*) ppm. The analytical and spectral data in $D_2O$ were published earlier [9].

## References


[1] a) Grout RJ (1975) Biological reactions and pharmaceutical uses of imidic acid derivatives. In: Patai S (ed) The Chemistry of Amidines and Imidates, chapter 6. Wiley, Interscience, London, p 255; b) Hofmann K (1953) The Imidazolines, 2-Imidazolidones, 2-Imidazolidinethiones, 2-Iminoimidazolidines, and Imidazolidines. In: Weissberger A (ed) Imidazole and Its Derivatives, part I, chapter VII. The Chemistry of Heterocyclic Compounds. Interscience, New York, p 213; c) Hartmann M, Isler H (1939) Arch exptl Path Pharmakol **192**: 141; Chem Abstr (1940) **34**: 4068[7]

[2] a) Tse WC, Boger DL (2004) Acc Chem Res **37**: 61; b) Lacy ER, Madsen EM, Lee M, Wilson WD (2003) DNA and RNA Binders. In: Demeunynck M, Bailly C, Wilson WD (eds) Small Molecule DNA and RNA Binders: From Synthesis to Nucleic Acid Complexes, vol. 2. Wiley-VCH Verlag, Weinheim, p 384; c) Chow CS, Bogdan FM (1997) Chem Rev **97**: 1489

[3] a) Diana GD (1973) J Med Chem **16**: 857; b) Takaishi T, Sugawara Y, Suzuki M (1972) Tetrahedron Lett 1873; c) Julia M, M$^{me}$Preau-Joseph N (1967) Bull Soc Chim France 4348; d) Nakamura S (1961) Chem Pharm Bull **9**: 641; e) Probst GV, Hoehn MM, Woods BL (1965) Antimicrob Agents Chemother 789; f) Arcamone F, Orezzi PG, Barbieri W, Nicolella V, Penco S (1967) Gazz Chim Ital **97**: 1097

[4] Neidle S, Kelland LR, Trent JO, Simpson IJ, Boykin DW, Kumar A, Wilson WD (1997) Bioorg Med Chem Lett **7**: 1403

[5] Klarer W, Urech E (1944) Helv Chim Acta **27**: 1762

[6] Marxer A (1957) J Am Chem Soc **79**: 467

[7] Perillo I, Caterina MC, Lopez J, Salerno A (2004) Synthesis 851

[8] a) Kyrides LP, Zienty FB, Steahly GW, Morrill HL (1947) J Org Chem **12**: 577; b) King JA, McMillan FH (1946) J Am Chem Soc **68**: 1774
[9] Spychala J (1999) Tetrahedron Lett **40**: 2841
[10] Spychala J (2003) Magn Reson Chem **41**: 169
[11] Spychala J (1997) Synth Commun **27**: 3431
[12] Spychala J (2000) Tetrahedron **56**: 7981
[13] a) Walter W, Voss J (1970) The Chemistry of Thioamides. In: Zabicky J (ed) The Chemistry of Amides, chapter 8. Wiley, Interscience, New York, p 383; b) Lovens Kemiske Fabrik ved A Kongsted. Dan. patents 62,889 and 63,112; Chem Abstr (1946) **40**: $4398^4$
[14] a) Forssel G (1892) Ber **25**: 2132; b) Forssell G (1891) Ber **24**: 1846; c) Wallach O (1891) Ann **262**: 354
[15] a) Minabe M, Suzuki K (1972) Bull Chem Soc Jpn **45**: 3196; b) Vink JAJ, Verheijdt PL, Cornelisse J, Havinga E (1972) Tetrahedron **28**: 5081; c) Kossmehl G, Hatscher KH, Manecke G (1975) Makromol Chem **176**: 539
[16] Spychala J (1997) Synth Commun **27**: 127