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ORIGINAL PAPER

A versatile synthesis of benzothieno-annelated 1,2-dihydropyridine and 1,2,3,4-tetrahydropyridine derivatives: the effect of the structure of benzothieno-annelated pyridinium salts on their reduction by sodium borohydride

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Abstract Benzothieno[2,3-*c*]pyridinium and benzothieno[2,3-*c*]quinolinium salts were synthesized either by quaternization of benzothieno[2,3-*c*]pyridines, or recyclization of benzothieno[2,3-*c*]pyrylium salts with primary amines. One-pot synthesis of benzothieno[3,2-*g*]indolizinium salts from 1-(3-chloropropyl)-benzothieno[2,3-*c*]pyrylium included consequent recyclization of the pyrylium core by ammonia into a pyridine intermediate and its further intramolecular quaternization reaction. Depending on the structure of benzothieno-annelated pyridinium salts, their reaction with sodium borohydride in methanol results in reduction of the pyridine core into tetrahydropyridine or dihydropyridine derivatives. Whereas reduction of benzothieno[2,3-*c*]pyridinium and benzothieno[3,2-*g*]indolizinium salts readily yields benzothieno-annelated tetrahydropyridines as a complex mixture of stereoisomers, reduction of benzothieno[2,3-*c*]quinolinium salts results in dihydropyridine derivatives. The structure of the latter, in particular, was confirmed by single-crystal X-ray diffraction analysis.

Keywords Pyrylium · Benzothienopyridinium · Benzothienoquinolinium · Benzothienoindolizinium · Alkylation · Reduction

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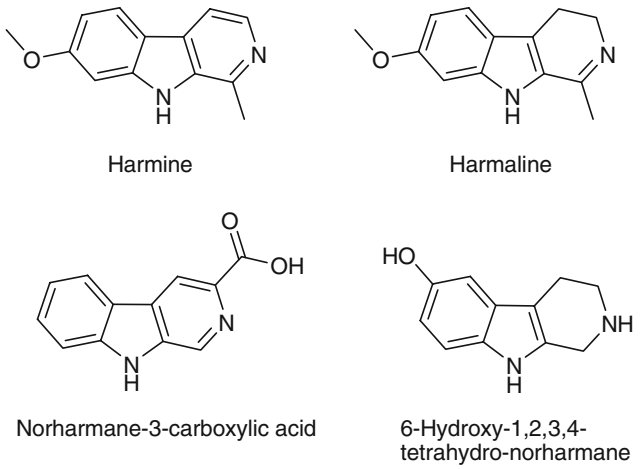
Introduction

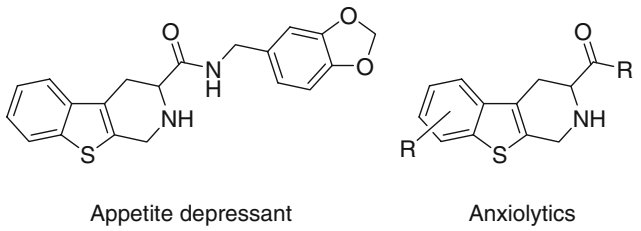
Natural β-carboline alkaloids, found in the seeds of *Peganum harmala* (Scheme 1), are of special interest because of their proven biological activity [1, 2]. Since the 1980s β-carbolines have become an important instrument in investigations of so called benzodiazepine receptors (BDR) [3]. The latter are the sites of allosteric regulation of γ-aminobutyric acid (GABA) receptors (Scheme 1).

High biological activity has also been demonstrated for a number of benzothieno[2,3-*c*]pyridine derivatives, i.e. S-isosters of β-carbolines [4]. Studies of biological activity of benzothiophene analogs of harmine and harmaline as monoamine oxidase (MAO) inhibitors in vitro showed that the activity of the S-analog of harmine is similar to that of harmine, and the S-analog of harmaline is even more efficient than harmaline itself [5–7]. The sulfur analogs of *Peganum harmala* alkaloids have higher solubility in lipids, shorter biological half-life, and weaker tissue binding than their nitrogen analogs [8, 9]. Tetrahydrobenzothieno[2,3-*c*]pyridine derivatives have been found to act as appetite-depressing agents [10], analgesics [11], anxiolytics, and antidepressants [9, 12] (Scheme 2).

Among synthetic approaches to 1,2,3,4-tetrahydro benzothieno[2,3-*c*]pyridines, the Pictet–Spengler cyclization of azomethines of 3-(2-aminoethyl)benzo[*b*]thiophenes is a common and widely used method [4, 13]. Another synthetic route includes Bischler–Napieralski cyclization of 3-(2-acetylaminoethyl)benzo[*b*]thiophenes affording 3,4-dihydrobenzothieno[2,3-*c*]pyridines, which can then be reduced into tetrahydro derivatives by sodium borohydride or lithium aluminum hydride [14]. To the best of our knowledge, *N*-substituted tetrahydrobenzothieno[2,3-*c*]pyridines are directly inaccessible by these methods.



Scheme 1



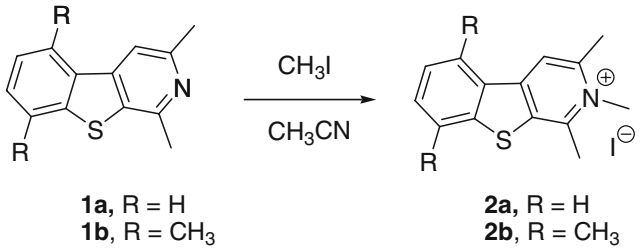
Scheme 2

Herewith we report the synthesis of 1,2,3-substituted benzothieno[2,3-*c*]pyridinium salts and their reduction by sodium borohydride in methanol. We demonstrate that, depending on the substituents at the pyridine core, benzothieno[2,3-*c*]pyridinium salts can undergo reduction to 1,2,3,4-tetrahydro- (**9a**–**9c**, **10**) or 1,2-dihydrobenzothieno[2,3-*c*]pyridine derivatives (**11c**–**11f**). Surprisingly, in the last case the keto-group is also left untouched.

Results and discussion

Synthetic and structural aspects

Three classes of benzothieno[2,3-*c*]pyridinium salts were prepared in order to investigate their applicability in the synthesis of tetrahydro derivatives and to determine how structural changes in the pyridinium core affect the reduction process. The desired pyridinium salts were obtained either by alkylation of benzothieno[2,3-*c*]pyridines, or by recyclization of benzothieno[2,3-*c*]pyrylium derivatives. Thus, readily available 1,3-dialkyl-substituted benzothieno[2,3-*c*]pyridines **1a**, **1b** [15] were successfully alkylated with methyl iodide in acetonitrile affording *N*-methyl derivatives **2a**, **2b** according to Scheme 3.



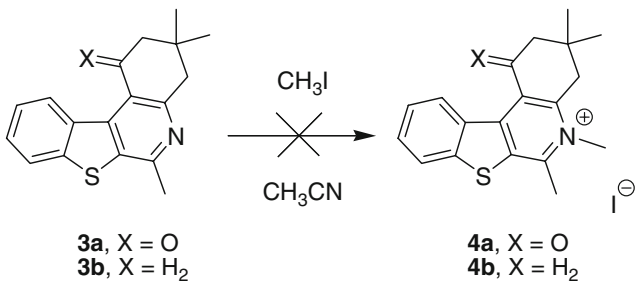
Scheme 3

However, application of this general alkylation procedure to 3,3,6-trimethyl-1,2,3,4-tetrahydrobenzothieno[2,3-*c*]quinolines **3a**, **3b** [16] did not lead to the expected salts **4a**, **4b**, when alkylated with methyl iodide in acetonitrile under conditions similar to those for compounds **2a**, **2b** (Scheme 4).

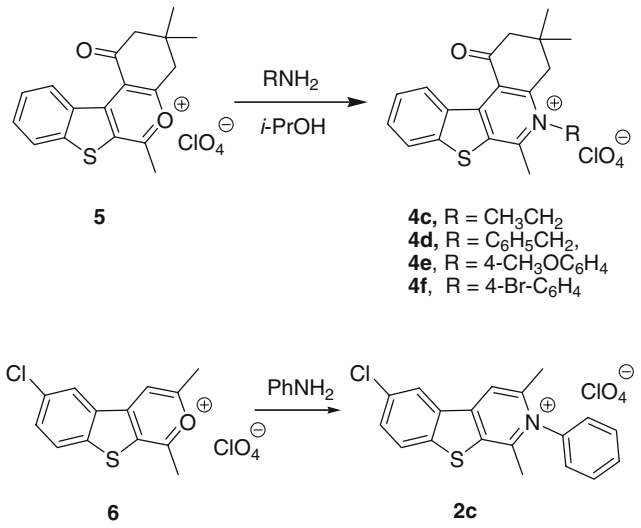
Therefore, to afford pyridinium salts **4** we used another approach, namely recyclization of pyrylium into pyridinium, using primary amines [17, 18]. We have previously described a convenient synthesis of 1-oxo-3,3,6-trimethyl-1,2,3,4-tetrahydrobenzothieno[2,3-*c*]pyrylium perchlorate **5** [16], which is a suitable starting material for the synthesis of pyridinium salts **4**. Heating **5** under reflux with one equivalent of primary amine in 2-propanol resulted exclusively in benzothieno[2,3-*c*]pyridinium salts **4c**–**4f** in 60–90% yields and no undesired 1-aminodibenzothiophene derivatives [19] were detected (Scheme 5). This reaction was successfully employed to gain access to not only *N*-alkyl pyridinium salts **4c**, **4d**, but also *N*-aryl pyridinium salts **4e**, **4f**, that are inaccessible by simple alkylation of pyridines. A similar recyclization to obtain *N*-aryl pyridinium salt **2c** was previously described [19].

We also prepared benzothieno[3,2-*g*]indolizinium salt **8** by tandem recyclization/quaternization [20] of pyrylium perchlorate **7** with ammonia [21] (Scheme 6).

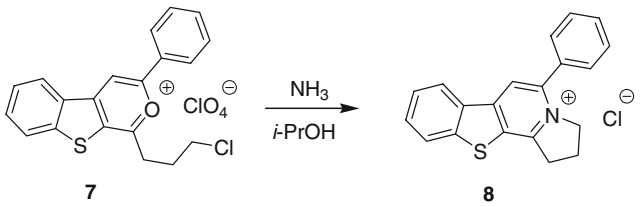
Our interest in indolizinium derivatives was particularly stimulated by a recent report on novel alkaloids with a pyrrolo[2,1-*a*]isoquinoline skeleton (Scheme 7) isolated from *Carduus crispus*, which is used in Chinese folk medicine for treatment of cold, stomach ache, and



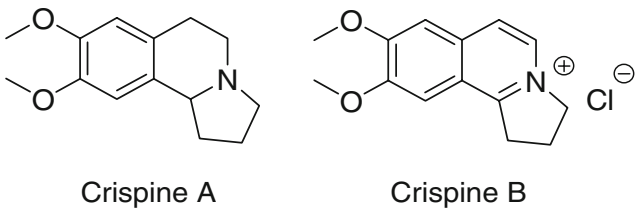
Scheme 4



Scheme 5



Scheme 6



Scheme 7

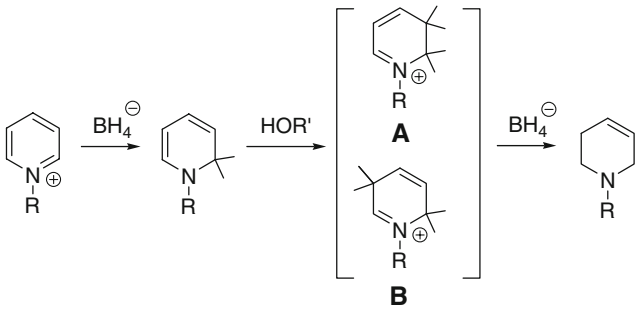
rheumatism [22]. It was shown that crispine B has cytotoxic activity against some human-cancer lines in vitro.

Reduction of benzothieno-annelated pyridinium salts **2a**–**2c**, **4c**–**4f**, and **8** was carried out with fivefold excess of sodium borohydride in methanol.

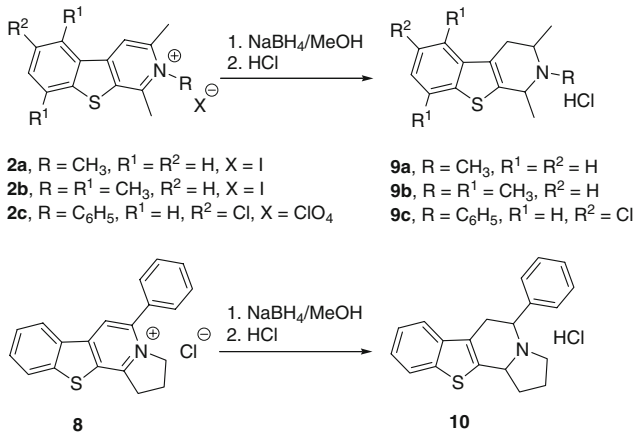
It is known that reduction of pyridinium salts by sodium borohydride results in a mixture of 1,2-dihydropyridines and 1,4-dihydropyridines [23–26]. The ratio of the isomers depends on the substituents in the pyridinium ring and the conditions used. Quinolinium salts undergo similar reduction by $NaBH_4$ to give a mixture of 1,2-dihydroquinolines and 1,4-dihydroquinolines, and 1,2-dihydroisomers usually predominate [27]. It should be noted that substituents at the nitrogen and carbon atoms of the pyridine core affect the stability of dihydropyridine derivatives towards further reduction, and in some cases the reaction results in 1,2,5,6-tetrahydropyridines [27–30]. Studying the mechanism of simple pyridinium ions reduction by sodium borohydride, Lyle et al. demonstrated that transformation of dihydropyridines into tetrahydropyridines involves their protonation to form intermediates **A** and **B** (Scheme 8) [31, 32].

We found that benzothieno[2,3-*c*]pyridinium salts **2a**–**2c** and benzothieno[3,2-*g*]indolizinium salts **8** readily undergo reduction to tetrahydro derivatives **9a**–**9c** and **10**, which were obtained in 60–80% yields and isolated as hydrochlorides (Scheme 9).

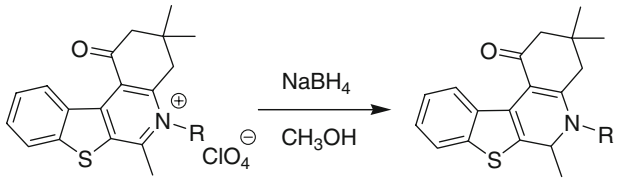
Compounds **9a**–**9c** and **10** have two chiral carbon centers and are mixtures of four stereoisomers. It is known that, in most cases, enantiomers can be distinguished in NMR spectra only by using suitable enantiomeric discrimination agents [33], but diastereomers might show up without special stereogenic treatment [34]. In our case, ^1H NMR spectra of **9a**–**9c** and **10** enabled estimation of the ratio between pairs of diastereomers in the obtained products. Thus, **9a** and **9c** are mixtures of two pairs of diastereoisomers in 2:1 ratio, whereas in **9b** the mixture is in 1:1 ratio. The ratio could not be estimated for **10**, because the signals from pairs of diastereomers overlapped.



Scheme 8



Scheme 9



4c, R = CH_3CH_2
4d, R = $C_6H_5CH_2$,
4e, R = 4-$CH_3OC_6H_4$
4f, R = 4-Br-C_6H_4

11c, R = CH_3CH_2
11d, R = $C_6H_5CH_2$,
11e, R = 4-$CH_3OC_6H_4$
11f, R = 4-Br-C_6H_4

Scheme 10

For pyridinium salts **4c**–**4f** the reduction proceeded differently, affording exclusively dihydro derivatives **11c**–**11f** (Scheme 10). Even when a 20-fold excess of sodium borohydride was used, no further reduction into tetrahydro derivatives and/or reduction of the carbonyl group were observed.

Because **11c**–**11f** have only one chiral center, two enantiomers are not distinguished by NMR under conditions that we used. ^{1}H NMR spectra of compounds **11c**–**11f** contained only one signal from the proton on the chiral carbon atom and one signal from the protons of the neighboring methyl group.

The increased stability of dihydro derivatives **11c**–**11f** towards further reduction into tetrahydro derivatives can be rationalized on the basis of enaminoketone fragment formation (and possibly because of steric hindrance). The formation of such conjugated enaminoketone moiety also causes a shift of the C=O absorption in the infrared spectra to high frequencies (1,615 cm^{-1} for **11f**) compared with that of the initial pyridinium salt **4f** (1,700 cm^{-1}). Such a shift is generally an indication of strongly conjugated carbonyl groups [35] and, for example, the pyrazolone moiety (formally containing the N–C=C–C=O fragment) was shown to be stable in the reduction reaction with $NaBH_4$ [36].

*Single-crystal X-ray structure of **11f***

Single-crystal X-ray diffraction analysis of compound **11f** provides confirmation that dihydropyridine derivatives are formed. As seen from Fig. 1, molecule **11f** is chiral. The (*R*) configuration has been assigned to the chiral center, in accordance with the Cahn–Ingold–Prelog rules.

The dihydropyridine ring adopts a conformation which is intermediate between sofa and twist-boat. The C(8)–C(7)–C(11)–C(10) and N(1)–C(10)–C(11)–C(7) torsion angles are −24.0(5) and 14.5(6)°. The C(9) and N(1) atoms deviate from the mean plane of the other atoms of the ring by −0.540 and 0.116 Å, respectively. The conformation of the cyclohexenone ring can be described as distorted sofa. The C(10), C(11), C(12), C(13), and C(15) atoms are coplanar within 0.04 Å and the C(14) atom lies at 0.65 Å from this plane.

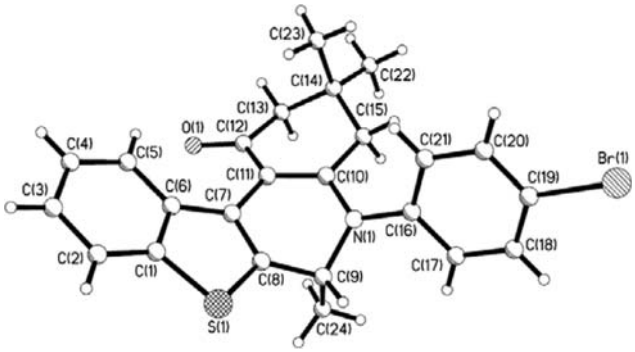


Fig. 1 Molecular structure of compound **11f**

The 4-bromophenyl substituent is rotated relative to the plane formed by the N(1) and linked atoms [C(9)–N(1)–C(16)–C(17) torsion angle is 47.0(5)°] because of steric factors (shortened intramolecular contacts C(21)···H(15B) of 2.60 Å, C(16)···H(15B) of 2.62 Å, C(17)···H(9) of 2.72 Å, and C(9)···H(17) of 2.81 Å; van der Waals radii sum is 2.87 Å [37]). This causes elongation of the N(1)–C(16) bond up to 1.418(5) Å and the mean value is 1.371 Å [38]. The presence of a bulky substituent on the N(1) atom results in axial orientation of the C(24) methyl group [the C(7)–C(8)–C(9)–C(24) torsion angle is −81.9(5)°].

Some bond elongation is observed for the C(10)–C(11) and O(1)–C(12) bonds [1.376(6) and 1.238(5) Å, and the mean values are 1.322 and 1.210 Å], probably because of strong conjugation within the N(1)–C(10)–C(11)-C(12)–O(1) fragment.

The carbonyl group participates in the formation of the intramolecular hydrogen bond C(5)–H(5)···O(1) (the H···O distance is 2.32 Å and the C–H···O angle is 128°). In the crystal, the molecules of **11f** form infinite chains along

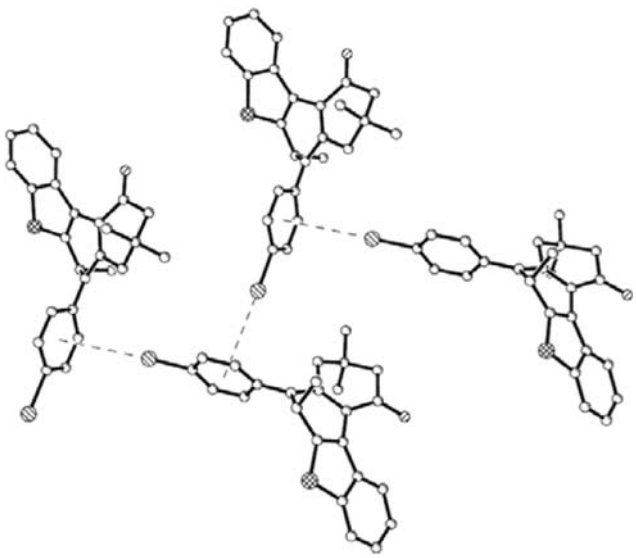


Fig. 2 Crystal packing of compound **11f**, hydrogen atoms are omitted for clarity

the (010) direction through the Br···π interactions (Fig. 2): the distance between Br(1) and the center of C(16)···C(21) ring is 3.69 Å, close to the van der Waals radii sum (3.68 Å).

Conclusions

In conclusion, benzothieno[2,3-*c*]pyridinium salts **2a**–**2c**, **4c**–**4f** and benzothieno[3,2-*g*]indolizinium salts **8** are convenient intermediates for synthesis of 1,2,3-substituted benzothieno-annelated heterocyclic systems with dihydropyridine and tetrahydropyridine moieties. We have shown that, depending on the structure of benzothieno-annelated pyridinium salts, their reaction with sodium borohydride in methanol results in reduction of the pyridine core into tetrahydropyridine or dihydropyridine rings. Reduction of pyridinium (**2a**–**2c**) and indolizinium salts (**8**) readily gives corresponding benzothieno-annelated tetrahydropyridines in good yields. Reduction of **4c**–**4f**, which contain cyclohexanone fragments attached to the pyridine ring, leads to dihydropyridine derivatives **11c**–**11f**. The single-crystal X-ray diffraction analysis of **11f** also confirms that the carbonyl group is not reduced. Studies of biological activity of the synthesized compounds are in progress and will be reported elsewhere.

Experimental

Melting points were determined in non-sealed capillaries using a Bellstone apparatus. The infrared spectra were recorded on a Specord IR-75 spectrometer from KBr pellets. The ^{1}H NMR spectra were recorded on Varian Gemini 200 (200 MHz), Bruker Avance 400 (400 MHz), and Bruker DRX 500 (500 MHz) NMR instruments, using TMS as an internal standard; assignments of protons were based on ^{1}H–^{1}H COSY NMR spectra. Mass spectra were acquired on HP 59980B and Micromass Autospec instruments, operating in electron-impact mode at 70 eV. CHNS elemental analyses were performed using a Fisons AE1108 analyzer and the results were found to be in good agreement (±0.25%) with the calculated values.

Benzothieno[2,3-*c*]pyridines **1a**, **1b** [15], benzothieno[2,3-*c*]pyridinium perchlorate **2c** [19], benzothieno[2,3-*c*]quinolines **3a**, **3b** [16], benzothieno[2,3-*c*]pyrylium perchlorates **5** [16] and **6** [19], and benzothieno[3,2-*g*]indolizinium chloride **8** [21] were obtained as reported elsewhere.

*General procedure for preparation of [1]benzothieno[2,3-c]pyridinium iodides **2a**, **2b***

To a solution of benzothieno[2,3-*c*]pyridine **1a**, **1b** (1.5 mmol) in 10 cm^3 acetonitrile a fivefold excess of methyl iodide (7.5 mmol) was added and the solution was heated under reflux for 24 h. The precipitate formed was isolated by filtration, washed successively with acetone and diethyl ether, and dried. The crude product was recrystallized from methanol.

1,2,3-Trimethyl[1]benzothieno[2,3-c]pyridinium iodide (**2a**, $C_{14}H_{14}INS$)
This compound was obtained in 70% yield as yellowish needles. M.p.: 258–259 °C; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 2.96$ (3H, s, 3-CH_3), 3.05 (3H, s, 1-CH_3), 4.24 (3H, s, *N*-CH_3), 7.71 (1H, t, $J = 8.0$ Hz, 6-H), 7.84 (1H, t, $J = 8.0$ Hz, 7-H), 8.24 (1H, d, $J = 8.0$ Hz, 5-H), 8.62 (1H, d, $J = 8.0$ Hz, 8-H), 8.84 (1H, s, 4-H) ppm.

1,2,3,5,8-Pentamethyl[1]benzothieno[2,3-c]pyridinium iodide (**2b**, $C_{16}H_{18}INS$)
This compound was obtained in 85% yield as yellow–green crystals. M.p.: 260–262 °C; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 2.59$ (3H, s, 3-CH_3), 2.93 (3H, s, 1-CH_3), 2.98 (3H, s, 5-CH_3), 3.12 (3H, s, 8-CH_3), 4.23 (3H, s, *N*-CH_3), 7.44 (1H, d, $J = 7.6$ Hz, 6-H), 7.59 (1H, d, $J = 7.6$ Hz, 7-H), 8.63 (1H, s, 4-H) ppm.

*General procedure for preparation of [1]benzothieno[2,3-c]quinolinium perchlorates **4c**–**4f***

To a stirred suspension of 0.7 g **5** (1.8 mmol) in 10 cm^3 2-propanol, one equivalent of the corresponding amine was added and the mixture was heated under reflux for 3 h. The precipitate formed was isolated by filtration, washed successively with 2-propanol, acetone, and diethyl ether, dried, and recrystallized from acetic acid.

5-Ethyl-1,2,3,4-tetrahydro-3,3,6-trimethyl-1-oxo[1]benzothieno[2,3-c]quinolinium perchlorate (**4c**, $C_{20}H_{22}ClNO_5S$)
This compound was obtained in 62% yield as a yellow powder. M.p.: 225–226 °C; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 1.22$ (6H, s, 3,3-CH_3), 1.55 (3H, t, $J = 7.0$ Hz, CH_3CH_2), 2.91 (2H, s, 2-CH_2), 3.24 (3H, s, 6-CH_3), 3.46 (2H, s, 4-CH_2), 4.81 (2H, q, $J = 7.0$ Hz, CH_3CH_2), 7.63 (1H, t, $J = 8.0$ Hz, 10-H), 7.87 (1H, t, $J = 8.0$ Hz, 9-H), 8.32 (1H, d, $J = 8.0$ Hz, 11-H), 8.72 (1H, d, $J = 8.0$ Hz, 8-H) ppm.

1,2,3,4-Tetrahydro-3,3,6-trimethyl-1-oxo-5-(phenylmethyl)-[1]benzothieno[2,3-c]quinolinium perchlorate (**4d**, $C_{25}H_{24}ClNO_5S$)
This compound was obtained in 75% yield as a yellow powder. M.p.: 247–248 °C; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 1.07$ (6H, s, 3,3-CH_3), 3.15 (3H, s, 6-CH_3), 3.23 (2H, s, 2-CH_2), 3.31 (2H, s, 4-CH_2), 6.14 (2H, s, $C_6H_5CH_2$), 7.11–7.29 (2H, m, 2,6-Ph), 7.30–7.55 (3H, m, 3,4,5-Ph), 7.67 (1H, t, $J = 7.0$ Hz, 10-H), 7.91 (1H, t,

$J = 7.0$ Hz, 9-H), 8.36 (1H, dd, $J = 7.5$ Hz, 2.2 Hz, 11-H), 8.79 (1H, dd, $J = 7.5$ Hz, 2.2 Hz, 8-H) ppm.

1,2,3,4-Tetrahydro-5-(4-methoxyphenyl)-3,3,6-trimethyl-1-oxo[1]benzothieno[2,3-c]quinolinium perchlorate (**4e**, $C_{25}H_{24}ClNO_6S$)

This compound was obtained in 60% yield as a yellow powder. M.p.: 259–260 °C; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 1.11$ (6H, s, 3,3-CH_3), 2.75 (3H, s, 6-CH_3), 2.82 (2H, s, 2-CH_2), 2.91 (2H, s, 4-CH_2), 3.95 (3H, s, OCH_3), 7.35 (2H, d, $J = 8.0$ Hz, 2,6-Ph), 7.63 (2H, d, $J = 8.0$ Hz, 3,5-Ph), 7.74 (1H, t, $J = 8.0$ Hz, 10-H), 7.96 (1H, t, $J = 8.0$ Hz, 9-H), 8.44 (1H, d, $J = 8.0$ Hz, 11-H), 8.91 (1H, d, $J = 8.0$ Hz, 8-H) ppm.

5-(4-Bromophenyl)-1,2,3,4-tetrahydro-3,3,6-trimethyl-1-oxo[1]benzothieno[2,3-c]quinolinium perchlorate (**4f**, $C_{24}H_{21}BrClNO_5S$)

This compound was obtained in 89% yield as a yellow powder. M.p.: 290–291 °C; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 1.08$ (6H, s, 3,3-CH_3), 2.74 (3H, s, 6-CH_3), 2.80 (2H, s, 2-CH_2), 2.89 (2H, s, 4-CH_2), 7.63–7.78 (3H, m, 2,6-Ph, 10-H), 7.88–8.11 (3H, m, 3,5-Ph, 9-H), 8.42 (1H, d, $J = 8.4$ Hz, 11-H), 8.89 (1H, d, $J = 8.4$ Hz, 8-H) ppm; IR (KBr): $\bar{\nu} = 3{,}400$, 2,943, 2,363, 2,333, 1,700, 1,595, 1,100 cm^{-1}.

1-(3-Chloropropyl)-3-phenyl[1]benzothieno[2,3-c]pyrylium perchlorate (**7**, $C_{20}H_{16}Cl_2O_5S$)

This compound was prepared by following the procedure similar one described previously [21]. To a solution of 1.5 g 2-(3-benzo[*b*]thienyl)-1-phenylethanone (6.0 mmol) in 10 cm^3 dichloroethane, 0.67 cm^3 4-chlorobutyryl chloride (6.0 mmol) and 0.80 g anhydrous $AlCl_3$ (6.0 mmol) were added with stirring at 10 °C. After stirring for 3 h at r.t., 0.60 cm^3 70% $HClO_4$ (6.0 mmol) was added dropwise. The precipitate was isolated by filtration, washed successively with aqueous isopropanol, isopropanol, and diethyl ether, and dried to afford 1.58 g (60%) product as an orange powder. M.p.: 212–213 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 2.71$ (2H, m, $CH_2CH_2CH_2Cl$), 3.81 (4H, t, $J = 6.0$ Hz, $CH_2CH_2CH_2Cl$), 7.63–7.81 (3H, m, 3,4,5-Ph), 7.86 (1H, t, $J = 8.0$ Hz, 6-H), 8.06 (1H, t, $J = 8.0$ Hz, 7-H), 8.14–8.30 (3H, m, 5-H, 2,6-Ph), 8.70 (1H, d, $J = 8.0$ Hz, 8-H), 8.94 (1H, s, 4-H) ppm.

*General procedure for sodium borohydride reduction of compounds **2a–2c** and **8***

To a stirred suspension of benzothieno[2,3-*c*]pyridinium salt **2a–2c** or **8** (2 mmol) in 10 cm^3 methanol a fivefold excess of sodium borohydride was added with care at room temperature, avoiding intense evolution of hydrogen. During the addition of $NaBH_4$ the pyridinium salt dissolved and, finally, the solution obtained was heated under reflux for 3 h. The solution was concentrated by evaporation, diluted with a large amount of water to dissolve the inorganic compounds, and the oily product was extracted with 3×20 cm^3 $CHCl_3$. Chloroform was removed under reduced pressure, the residue was dissolved in 10 cm^3 acetone, and 0.2 cm^3 (2 mmol) of conc. HCl was added. The precipitate was isolated by filtration, washed successively with dry acetone and diethyl ether, and dried. The crude product was recrystallized from methanol.

1,2,3,4-Tetrahydro-1,2,3-trimethyl[1]benzothieno[2,3-c]pyridine hydrochloride (**9a**, $C_{14}H_{18}ClNS$)

This compound was obtained from salt **2a** in 60 % yield as light-yellow crystals. M.p.: 195–197 °C. According to its ^{1}H NMR spectrum, this product is a mixture of two pairs of diastereoisomers in 2:1 ratio (accordingly, two sets of ^{1}H NMR shifts are given in parentheses; the first set is for the major isomer). ^{1}H NMR (500 MHz, DMSO-d_6): $\delta =$ [(1.66, d, $J = 6.7$ Hz) and (1.56, d, $J = 6.7$ Hz), 3H, 3-CH_3], [(1.80, d, $J = 6.7$ Hz) and (1.90, d, $J = 6.7$ Hz), 3H, 1-CH_3], [(2.54, d, $J = 4.8$ Hz) and (2.97, d, $J = 4.8$ Hz), 3H, *N*-CH_3], 2.78–2.90 (1H, m, 4-CH_2), 3.11–3.22 (1H, m, 4-CH_2), [(3.99–4.11, m) and (3.65–3.74, m), 1H, 3-CH], [(5.04–5.12, m) and (4.68–4.75, m), 1H, 1-CH], 7.33–7.45 (2H, m, 5,6-H), 7.68 (1H, d, $J = 8.0$ Hz, 8-H), 7.87 (1H, t, $J = 8.0$ Hz, 7-H), [(12.98, br s) and (12.57, br s), 1H, N^+-H] ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 19.91$, 32.77, 33.35, 35.85, 55.63, 58.03, 123.91, 126.54, 126.96, 128.22, 129.19, 131.32, 138.61, 139.34 ppm; MS (EI, 70 eV): $m/z = 231$ (M^+), 216 (M^+-CH_3).

1,2,3,4-Tetrahydro-1,2,3,5,8-pentamethyl[1]benzothieno[2,3-c]pyridine (**9b**, $C_{16}H_{21}NS$)

This compound was obtained from salt **2b** in 72 % yield as yellow crystals. M.p.: 175–177 °C. **9b** was then converted into the base for further characterization. To achieve this, it was dissolved in warm water and excess $NaHCO_3$ was added. The milk-like solution formed was extracted with diethyl ether (3×20 cm^3), organic extracts were dried over $MgSO_4$, the solvent was then evaporated, and the residue was dried in vacuo to afford the base of **9b** as a light-yellow oil. According to its ^{1}H NMR spectrum, **9b** is a mixture of two pairs of diastereoisomers in 1:1 ratio (accordingly, two sets of ^{1}H NMR shifts are given in parentheses). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta =$ [(1.24, d, $J = 6.8$ Hz) and (1.35, d, $J = 6.8$ Hz), 3H, 3-CH_3], [(1.55, d, $J = 6.8$ Hz) and (1.60, d, $J = 6.8$ Hz), 3H, 1-CH_3], [(2.34, s) and (2.44, s), 3H, 5-CH_3], 2.49 (3H, s, 8-CH_3), 2.70 (3H, d, $J = 3.6$ Hz, *N*-CH_3), [(2.81–2.96, m) and (3.28–3.40, m), 2H, 4-CH_2], 3.03–3.22 (1H, m, 3-CH), 3.88–4.04 (1H, m, 1-CH), 6.97 (1H, d, $J = 7.4$ Hz, 6-H), 7.01 (1H, d, $J = 7.4$ Hz, 7-H) ppm; ^{13}C NMR (125 MHz,

$CDCl_3$): $\delta = 19.88$, 20.46, 20.81, 31.98, 33.05, 34.68, 55.77, 58.53, 123.70, 126.73, 126.76, 128.61, 129.29, 130.52, 133.71, 139.94 ppm; MS (EI, 70 eV): $m/z = 259$ (M^+), 244 (M^+-CH_3).

6-Chloro-1,2,3,4-tetrahydro-1,3-dimethyl-2-phenyl[1]benzothieno[2,3-c]pyridine hydrochloride (**9c**, $C_{19}H_{19}Cl_2NS$)

This compound was obtained from salt **2c** in 52% yield as yellowish crystals. M.p.: 204–206 °C. According to its ^{1}H NMR spectrum, this product is a mixture of two stereoisomers in 2:1 ratio (accordingly, two sets of ^{1}H NMR shifts are given in parentheses; the first set is for the major isomer). ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 1.25$ (3H, d, $J = 6.0$ Hz, 3-CH_3), 1.56 (3H, d, $J = 6.0$ Hz, 1-CH_3), 3.21–3.74 (2H, m, CH_2), [(4.28–4.44, m) and (4.07–4.20, m), 1H, 3-CH], [(5.23–5.39, m) and (5.00–5.14, m), 1H, 1-CH], [(7.37, d, $J = 8.5$ Hz) and (7.32, d, $J = 8.5$ Hz), 1H, 8-H], 7.41–7.66 (5H, m, Ph), [(7.77, s) and (7.68, s), 1H, 5-H], [(7.90, d, $J = 8.5$ Hz) and (7.85, d, $J = 8.5$ Hz), 1H, 7-H], 14.45 (1H, br s, N^+-H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 18.05$, 23.18, 24.90, 29.47, 38.45, 120.93, 121.14, 123.70, 124.29, 124.40, 125.02, 127.00, 129.77, 130.01, 136.53, 136.73, 138.99 ppm; MS (EI, 70 eV): $m/z = 327$ (M^+), 312 (M^+-CH_3).

1,2,3,5,6,11b-Hexahydro-5-phenyl[1]benzothieno[3,2-g]indolizine hydrochloride (**10**, $C_{20}H_{20}ClNS$)

This compound was obtained from salt **8** in 81% yield as rose crystals. M.p.: 299–301 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 1.88$–2.29 (3H, m, 6-C*H*H, 2-CH_2), 2.58–2.72 (1H, m, 6-CH*H*), 2.89–3.07 (1H, m, 1-C*H*H), 3.33–3.46 (3H, m, 1-CH*H*, 3-CH_2), 4.67–4.83 (1H, m, 11b-CH), 5.02–5.18 (1H, m, 5-CH), 7.39–7.61 (5H, m, 3,4,5-Ph, 8,9-H), 7.75–7.84 (1H, dd, $J = 8.6$ Hz, 2.5 Hz, 7-H), 7.87–7.96 (2H, d, $J = 7.1$ Hz, 2,6-Ph), 7.99–8.09 (1H, dd, $J = 8.6$ Hz, 2.5 Hz, 10-H), 12.74 (1H, br s, N^+-H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 22.00$, 30.06, 30.42, 51.39, 60.87, 62.26, 121.74, 122.72, 124.73, 125.02, 127.56, 128.63, 129.06, 129.24, 131.58, 135.73, 137.00, 138.27 ppm; MS (EI, 70 eV): $m/z = 305$ (M^+), 228 (M^+-C_6H_5).

*General procedure for sodium borohydride reduction of compounds **4c–4f***

To a suspension of the pyridinium salt **4c**–**4f** (3 mmol) in 10 cm^3 methanol, 20-fold excess of sodium borohydride was added with care at room temperature, avoiding intense evolution of hydrogen. During addition of $NaBH_4$ the pyridinium salt dissolved and, finally, the solution formed was heated under reflux for 3 h. The solution was concentrated and diluted with a large amount of water. The precipitate was isolated by filtration, washed with water, dried, and recrystallized from 10:1 2-propanol–water.

5-Ethyl-3,4,5,6-tetrahydro-3,3,6-trimethyl[1]benzothieno[2,3-c]quinolin-1(2H)-one (**11c**, $C_{20}H_{23}NOS$)

This compound was obtained from salt **4c** in 78% yield as white crystals. M.p.: 186–187 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.15$ (3H, s, 3-CH_3), 1.16 (3H, s, 3-CH_3), 1.26 (3H, t, $J = 7.1$ Hz, CH_3CH_2), 1.39 (3H, d, $J = 6.3$ Hz, 6-CH_3), 2.24 (1H, d, $J = 16.2$ Hz, 4-CH_2), 2.30 (1H, d, $J = 16.2$ Hz, 4-CH_2), 2.46 (1H, d, $J = 16.6$ Hz, 2-CH_2), 2.57 (1H, d, $J = 16.6$ Hz, 2-CH_2), 3.39–3.48 (1H, m, CH_3C*H*H), 3.59–3.68 (1H, m, CH_3CH*H*), 4.86 (1H, q, $J = 6.4$ Hz, 6-H), 7.16–7.25 (2H, m, 9,10-H), 7.69 (1H, dd, $J = 8.7$ Hz, 1.9 Hz, 11-H), 8.13 (1H, dd, $J = 8.7$ Hz, 1.9 Hz, 8-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 15.32$, 20.14, 27.67, 29.65, 31.81, 41.05, 44.99, 50.45, 55.99, 107.44, 122.02, 123.80, 123.87, 126.65, 126.87, 128.50, 136.54, 139.55, 157.51, 190.50 ppm; MS (EI, 70 eV): $m/z = 325$ (M^+), 310 (M^+-CH_3).

3,4,5,6-Tetrahydro-3,3,6-trimethyl-5-(phenylmethyl)[1]benzothieno[2,3-c]quinolin-1(2H)-one (**11d**, $C_{25}H_{25}NOS$)

This compound was obtained from salt **4d** in 63% yield as white crystals. M.p.: 171–173 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.04$ (3H, s, 3-CH_3), 1.12 (3H, s, 3-CH_3), 1.40 (3H, d, $J = 6.4$ Hz, 6-CH_3), 2.29 (2H, s, 4-CH_2), 2.47 (1H, d, $J = 16.9$ Hz, 2-CH_2), 2.57 (1H, d, $J = 16.9$ Hz, 2-CH_2), 4.61 (1H, d, $J = 16.8$ Hz, C_6H_5C*H*H), 4.83 (1H, q, $J = 6.4$ Hz, 6-H), 4.95 (1H, d, $J = 16.8$ Hz, C_6H_5CH*H*), 7.15 (2H, d, J = 7.6 Hz, 2,6-Ph), 7.18–7.34 (5H, m, 9,10-H, 3,4,5-Ph), 7.70 (1H, d, $J = 8.0$ Hz, 11-H), 8.18 (1H, d, $J = 8.0$ Hz, 8-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.09$, 28.05, 28.59, 32.84, 43.02, 51.35, 53.48, 58.71, 108.19, 114.61, 122.09, 123.85, 126.11, 126.51, 127.02, 127.89, 128.94, 129.13, 136.36, 136.62, 139.76, 157.52, 191.08 ppm; MS (EI, 70 eV): $m/z = 387$ (M^+), 372 (M^+-CH_3).

3,4,5,6-Tetrahydro-5-(4-methoxyphenyl)-3,3,6-trimethyl[1]benzothieno[2,3-c]quinolin-1(2H)-one (**11e**, $C_{25}H_{25}NO_2S$)

This compound was obtained from salt **4e** in 69% yield as white crystals. M.p.: 173–174 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.05$ (3H, s, 3-CH_3), 1.07 (3H, s, 3-CH_3), 1.53 (3H, d, $J = 6.4$ Hz, 6-CH_3), 2.18 (1H, d, $J = 16.8$ Hz, 2-CH_2), 2.24–2.31 (2H, m, 4-CH_2), 2.38 (1H, d, $J = 16.8$ Hz, 2-CH_2), 3.84 (3H, s, OCH_3), 5.00 (1H, q, $J = 6.5$ Hz, 6-H), 6.95 (2H, d, $J = 9.0$ Hz, 2,6-Ph), 7.19 (2H, d, $J = 8.5$ Hz, 3,5-Ph), 7.21–7.29 (2H, m, 9,10-H), 7.72 (1H, d, $J = 8.0$ Hz, 11-H), 8.16 (1H, d, $J = 8.0$ Hz, 8-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 20.99$, 27.95, 28.65, 32.52, 43.01, 51.28, 55.86, 58.88, 109.63,

114.83, 122.08, 123.83, 123.94, 126.01, 126.75, 128.47, 129.55, 136.36, 136.45, 139.52, 156.98, 158.82, 192.00 ppm; IR (KBr): $\bar{\nu}$ = 3,441, 3,053, 2,954, 2,867, 2,833, 1,617, 1,562, 1,537, 1,455, 1,424, 1,378, 1,365, 1,295, 1,272, 1,248, 1,172, 1,102, 1,076, 1,061, 1,033 cm^{-1}; MS (EI, 70 eV): m/z = 403 (M^+), 388 (M^+-CH_3).

5-(4-Bromophenyl)-3,4,5,6-tetrahydro-3,3,6-trimethyl[1]benzothieno[2,3-c]quinolin-1(2H)-one (**11f**, $C_{24}H_{22}BrNOS$)

This compound was obtained from salt **4f** in 75% yield as light-brown crystals. M.p.: 209–211 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.07 (3H, s, 3-CH_3), 1.11 (3H, s, 3-CH_3), 1.55 (3H, d, J = 6.5 Hz, 6-CH_3), 2.17 (1H, d, J = 16.4 Hz, 4-CH_2), 2.30 (1H, d, J = 16.0 Hz, 2-CH_2), 2.47 (1H, d, J = 16.4 Hz, 4-CH_2), 2.51 (1H, d, J = 16.0 Hz, 2-CH_2), 5.09 (1H, q, J = 6.5 Hz, 6-H), 7.18–7.30 (4H, m, 3,5-Ph, 9,10-H), 7.56 (2H, d, J = 8.5 Hz, 2,6-Ph), 7.73 (1H, d, J = 8.0 Hz, 11-H), 8.11 (1H, d, J = 8.0 Hz, 8-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.12, 28.15, 28.30, 33.24, 43.03, 51.56, 58.49, 111.90, 120.62, 122.15, 123.98, 124.06, 125.63, 126.55, 127.95, 130.12, 132.79, 136.19, 139.41, 142.71, 155.16, 192.73 ppm; IR (KBr): $\bar{\nu}$ = 3,400, 2,920, 2,850, 2,320, 2,350, 1,615, 1,505, 1,480, 1,400, 1,390, 1,360, 1,270, 1,250, 1,180, 1,140, 1,095, 1,075, 1,005 cm^{-1}; MS (EI, 70 eV): m/z = 451 (M^+, ^{79}Br), 453 (M^+, ^{81}Br), 436 (M^+-CH_3, ^{79}Br), 438 (M^+-CH_3, ^{81}Br).

Crystals suitable for single-crystal X-ray analysis were grown in a closed vial from a toluene–*n*-hexane mixture (1:2). Crystals of **11f** are monoclinic, $C_{24}H_{22}NOSBr$, at 20 °C a = 9.561(3) Å, b = 10.216(3) Å, c = 11.014(3) Å, β = 107.82(2)°, V = 1,024.3(5) $Å^3$, M_r = 452.40, Z = 2, space group $P2_1$, d_{calc} = 1.467 g/cm^3, $\mu(MoK_\alpha)$ = 2.123 mm^{-1}, $F(000)$ = 464. Unit cell dimensions and intensity of 2,006 reflections (1,888 unique, R_{int} = 0.020) were measured using an automatic four-circle Siemens P3/PC diffractometer (MoK_α, graphite monochromator, 2Θ/Θ-scan, $2\Theta_{max}$ = 50°). Structure was solved by direct method using the SHELX-97 software package [39]. The positions of the hydrogen atoms were located from difference maps of electron density and refined using a riding model with $U_{iso} = nU_{eq}$ of non-hydrogen atom bonded with hydrogen atom given (n = 1.5 for methyl groups and n = 1.2 for remaining H-atoms). Structure was refined by full-matrix, least-squares methods using anisotropic thermal parameters for all non-hydrogen atoms. Final divergence factors are wR_2 = 0.086 for 1,867 reflections (R_1 = 0.037 for 1,622 reflections with $F > 4\sigma(F)$, S = 1.04). Absorption correction was made semiempiricaly using Ψ-scan data (T_{min} = 0.448, T_{max} = 0.542). Absolute structure was established according to Flack parameter value 0.00(1).

Tables of atomic coordinates, bond lengths and angles, anisotropic displacement parameters, hydrogen coordinates, and isotropic displacement parameters have been deposited at the Cambridge Crystallographic Data Centre, CCDC No. 267307. These data can be obtained free of charge from the CCDC via http://www.ccdc.cam.ac.uk/data_request/cif.

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