Synthesis of some New Schiff Bases and Hydrazones Containing Benzonaphthyridine/ Benzonaphthyridone Moiety

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ABSTRACT

The N-(4-methyl-2-pyridyl)anthranilic acid (I) was synthesized by Ullmann condensation. The compound (I) was cyclized by polyphosphoric acid (PPA) to give 4-methyl-10H-benzo[b][1,8]naphthyridin-5-one (II). The compound (II) was treated with selenium dioxide (SeO₂) and thionyl chloride (SOCl₂) to give the 4-formyl-10H-benzo[b][1,8]naphthyridin-5-one (III) and 4-methyl-5-chloro-benzo[b][1,8]naphthyridine (IV) respectively. The compound (III) was reacted with various substituted anilines and aliphatic amines to give the Schiff bases (Va-j). The compound (IV) was reacted with hydrazine hydrate to yield the 5-hydrazino derivative (VI), which was reacted with various aromatic aldehydes to yield the hydrazones (VIIa-j) and the Rf values reported. The reaction progress was followed by thin layer chromatography (TLC). The synthesized compounds were confirmed by spectral data (I.R, ¹H-NMR, ¹³C-MNR). The possible fragmentation pattern of GC/MS for the compounds (III), (Vc) and (VIIg) were reported.

INTRODUCTION

Many Benzonaphthyridine derivatives have current interest due to their planner linear structure (Ivanove et al., 2005). Ullmann synthesis involves the condensation of o-halobenzoic acid with substituted 2-aminopyridine in presence of cupric oxide and anhydrous potassium carbonate to give N-pyridylanthranilic acids (Jameel and Al-Hadedi, 2010). Cyclization of N-pyridylanthranilic acid can be achieved by concentrated H₂SO₄ (Acheson, 1973), polyphosphoric acid (PPA) (Meftah et al., 1994) and POCl₃ (Al-Hadedi, 2008) to give different types of tricyclic hetero compounds. The literatures showed that the benzonaphthyridine/ benzonaphthyridone derivatives have versatile biological activities such as antitumor (Chen et al., 1994), trypanocidal (Meftah et
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al., 1994), antimicrobial (Tabart et al., 2001), antibacterial (Tabart et al., 2003), anticancer (Deady et al., 2003), anticolinesterase (Marco et al., 2004), antimalarial (Gorlitzer et al., 2007), anti-HSV-1 (Pincheiro et al., 2008), antifungal (Bhambi et al., 2009), anti-intestinal activity (Duan et al., 2011), and used as anti-inflammatory agent (Flockerzi et al., 2012). A new series of benzonaphthyridine/ benzonaphthyridone derivatives containing fused ring, such as imidazo (pyridino) group (Ming et al., 2011), pyrazolo group (Bernardino et al., 2012), were designed and synthesized.

In our previous work, a new benzonaphthyridine and benzonaphthyridone derivatives were synthesized, mainly sulpha drug-benz[b][1,8]naphthyridine (Al-Hadedi, 2008), 10H-benzo[b][1,8]naphthyridin-5-one hydrazones (Al-Hadedi, 2009; Al-Obaydee, 2010) and 10-(alkyl, alkylhalide, benzoyl)benzo[b][1,8]naphthyridin-5-one (Al-Obaydee, 2010). The aim of the present study is preparation of new Schiff bases and hydrazones derivatives containing benzonaphthyridine/ benzonaphthyridone which were expected to be biologically active compounds.

EXPERIMENTAL

Melting points were determined on an electrothermal IA 9300 Digital-series (1998) apparatus, and they were uncorrected. Infrared spectra were recorded on a Bruker FT-IR spectrophotometer Tensor 27, Germany (College of Education, University of Mosul). $^1$H, $^{13}$C-NMR spectra were recorded on a Bruker 300 MHz, in (Al-Al-Bayt University, Jordan) using TMS as an internal reference, and DMSO-$d_6$ as a solvent, and coupling constant J(Hz) with the use of the following abbreviations: s, singlet; d, doublet; t, triplet; m, multiplet and br, broad. Mass spectra (MS) were obtained from perkin Elmer Clarus 500 Gas chromatography-Mass spectrometer in (I.I.T Roorkee, Chemistry Dept., India), and from a trace 2000 series GC-MS in CH$_2$Cl$_2$ University of Southampton, Chemistry Dept., UK).

Preparation of N-(4-methyl-2-pyridyl)anthranilic acid (I).

This compound was prepared by the procedure reported in the previous work (Jameel and Al-Hadedi, 2010).

Preparation of 4-Methyl-10H-benzo[b][1,8]naphthyridin-5-one (II).

This compound was prepared by the procedure reported in the previous work (Al-Hadedi, 2009; Al-Obaydee, 2010).

Preparation of 4-formyl-10H-benzo[b][1,8]naphthyridin-5-one (III). (Chen and Deady, 1993).

In a 100 ml three-necked flask with sealed stirrer, a reflux condenser and a thermometer, 15 ml of dioxane was placed, then (1.32 g, 0.0119 mol) of selenium dioxide SeO$_2$ and (1 ml) water was added to the flask. The mixture was heated to 50-55°C until the solid was dissolved. The thermometer was removed and (2.5 g, 0.0119 mol) of compound (II) was added in one portion. The mixture was refluxed with stirring for 4 hrs. The progress of the reaction was monitored by TLC. The hot solution was decanted from the precipitated (black) selenium through fluted filter paper. The dioxane and water were removed by distillation to give a solid product. The product was recrystallized from ethanol to yield a brown powder, m.p = 170-172 °C, R$_f$ = 0.62, yield 2.2 g (83%).

Preparation of 4-[(1E)-(aryl or alkylimino)methyl]-10H-benzo[b][1,8]naphthyridine-5-one, (Va-j). (kannappan et al., 2009).

General procedure.

In a 25 ml dry methanol, (0.1 g, 0.00044 mol) of III was dissolved by stirring and mixed with (0.00044 mol) of appropriate amine. The solution was refluxed with stirring for at least 6 hrs. The progress of the reaction was monitored by TLC. The mixture was cooled and left overnight to complete the precipitation. The product was filtered off and dried in air. Table (1) summarizes the physical data for compounds Va-j.
Table 1: Some physical data for compounds Va-j.

| Compd. No. | R               | m,p °C | Rf*   | Color     | Yield % |
|------------|-----------------|--------|-------|-----------|---------|
| Va         | 4-CH₃C₆H₄-      | 241-242| 0.27  | Yellow    | 50      |
| Vb         | 3-CH₃C₆H₄-      | 232-236| 0.22  | Pale yellow| 42      |
| Vc         | 3,4-diCH₃C₆H₃-  | 234-230| 0.21  | Yellow    | 55      |
| Vd         | 2-NO₂C₆H₄-      | > 340  | 0.15  | Red       | 42      |
| Ve         | 4-NO₂C₆H₄-      | 278-280| 0.23  | Red       | 40      |
| Vf         | 2-NH₂C₆H₄-      | 250-252| 0.11  | Pale black| 40      |
| Vg         | CH₃CH₂CH₂-      | 171-173| 0.21  | Brown     | 45      |
| Vh         | CH₃CH₂CH₂CH₂-   | 179-181| 0.2   | Brown     | 47      |
| Vi         | CH₃CH₂CH₂CH₂CH₂-| 187-189| 0.2   | Brown     | 47      |
| Vj         | NH₂             | 199-201| 0.6   | Orange    | 35      |

* Elution solvent = CHCl₃:MeOH (9.5:0.5).

Preparation of 5-chloro-4-methylbenzo[b][1,8]naphthyridine (IV). (Atwell et al., 1984).

A mixture of (2.5 g, 0.012 mol) of compound II with excess (30 ml) of SOCl₂ containing (2 drops) DMF was refluxed for 3 hrs. The excess SOCl₂ was distilled off under reduced pressure, then the deep scarlet thick residue was diluted with cold chloroform, 150 ml (needs 2 hrs). The solution was slowly added with vigorous stirring to cold ammonia solution. The chloroform layer was separated and the aqueous alkaline solution was further extracted with (30ml×2) of chloroform. The combined chloroform extracts were dried by magnesium sulfate for overnight. The Chloroform filtrate was evaporated until dryness. The solid residue was recrystalyzed from ethanol to yield a brown powder, m.p = 116 - 118 °C. Rf = 0.95, (CHCl₃:MeOH, 9.5:0.5), yield 85%. (Lit. Al-Hadedi, 2009), 118-120 °C, Rf = 0.66.

Preparation of N-{4-methylbenzo[b][1,8]naphthyridin-5-yl}hydrazine (VI). (Chandra et al., 2010; Al-Hadedi, 2009).

Compound IV(3g) was added with stirring to the refluxing solution of hydrazine hydrate (30 ml, 80%) in (150 ml) ethanol during 10 min, and the refluxing continued for 40 min. The completion of the reaction was monitored by TLC. The solvent was distilled under reduced pressure, then extracted by chloroform (100ml×3), and dried by magnesium sulfate overnight. Filtration and evaporation of the solvent to dryness, recrystilazation from ethanol to yield a brown powder, m.p = 103-105 °C, Rf = 0.34 (CHCl₃: MeOH, 9.5:0.5), yield 90%. (Lit. Al-Hadedi, 2009), m. p = 103-105 °C, Rf = 0.31, yield 73%.

Preparation of substituted (1E)-benzyliden-N-{4-methylbenzo-[b][1,8]naphthyridin-5-yl}hydrazine, (VIIa-j). (Kannappan, et al., 2009).

General procedure

A mixture of (0.1 g, 0.00044 mol) of VI in 25 ml of methanol was mixed with (0.00044 mol) of appropriate aldehydes. The solution was refluxed with stirring for at least 6 hrs. The progress of the reaction was monitored by TLC. The mixture was cooled and left overnight to complete the fine precipitation. The product was filtered off and dried in air. Table (2) summarizes the physical data for compounds VIIa-j.
Table 2: Some physical data for compound VIIa-j

| Compd. No. | Ar          | m.p °C   | Rf  | Color         | Yield % |
|------------|-------------|----------|-----|---------------|---------|
| VIIa       | C₆H₅        | 110-111  | 0.89| Yellow        | 45      |
| VIIb       | 4-CH₃C₆H₄  | 158-160  | 0.96| Pale yellow   | 42      |
| VIIc       | 2-HOC₆H₄    | 218-220  | 0.91| Yellow crystal| 40      |
| VIId       | 4-BrC₆H₄    | 228-229  | 0.95| Pale yellow   | 50      |
| VIIe       | 4-NO₂C₆H₄   | 220-222  | 0.42| Yellow        | 70      |
| VIIf       | 3-NO₂C₆H₄   | 128-129  | 0.43| Pale yellow   | 55      |
| VIIg       | 4-ClC₆H₄    | 210-211  | 0.92| Pale yellow   | 38      |
| VIIh       | 4-MeOC₆H₄   | 169-170  | 0.89| Yellow        | 40      |
| VIIi       | 4-HO, 3-MeOC₆H₃ | 290 dec. | 0.85| Brown        | 41      |
| VIIj       | C₆H₅-CH=CH-  | 150 sub. | 0.57| Yellow        | 48      |

Elution solvent = CHCl₃:MeOH (9.5:0.5). dec. = decomposition; sub. = sublimation

Scheme (1)

RESULTS AND DISCUSSION

The methyl group in compound (II) was easily oxidized to the corresponding formyl group to form the compound III as shown in Scheme 1. (Chen and Deady, 1993; Deady et al., 2003). The
The structure of compound III was confirmed via IR spectrum which showed characteristic absorption peaks in the region (3479 cm\(^{-1}\)) due to the stretching of (N-H) bond, (1705 cm\(^{-1}\)) due to the stretching of (C=O) bond of the aldehyde group, (1687 cm\(^{-1}\)) due to stretching of (C=O) bond of the ketone group, and (1637 cm\(^{-1}\)) due to stretching of (C=N) bond. The \(^1\)H-NMR and \(^{13}\)C-NMR spectral data of compound III confirmed the above results, and showed the following significant peaks: multiplet at 7.13-7.25 for 1H (H-9), multiplet at 7.43-7.65 for 2H (H-7, H-8), multiplet at 7.78-7.91 for 2H (NH, H-6), multiplet at 8.11-8.29 for 1H (H-3), multiplet at 8.64-8.77 for 1H (H-2), singlet at 10.06 for 1H (C=O). The \(^{13}\)C-NMR spectral data of the compound III showed the following significant peaks: 111.09 (C\(_3\)), 115.72(C\(_{5a}\)), 111.64 (C\(_9\)), 116.7(C\(_{4a}\)), 117.05(C\(_7\)), 128.32(C\(_6\)), 134.06(C\(_8\)), 140.06(C\(_4\)), 146.98(C\(_{9a}\)), 148.28(C\(_2\)), 158.95(C\(_{10a}\)), 164.79(C\(_5\)), 191.93 (C\(_1\)). The mass spectral data Fig. (1) confirmed the above structure. The possible fragments (m/z) with their relative abundance (%) was reported as shown in Scheme (2). Similar data were found in Lit (Tian et al., 2012)

Scheme 2: Fragmentation pattern of compound (III)

The compounds Va-j (Deyanov and Konshin., 2004., Yi et al., 2008), have been prepared through the condensation of compound III with various substituted anilines or alkylamines. The structure of the prepared compounds Va-j, was elucidated by means of physical data Table (1) (m.p, Rf) and spectral data (Table 3). The IR spectra for compounds Va-j showed a characteristic absorption bands at (3473-3255 cm\(^{-1}\)) due to stretching of (N-H) bond, (1695-1682 cm\(^{-1}\)) due to stretching of (C=O) bond, (1645-1649 cm\(^{-1}\)) stretching of (C=N) bond. The \(^1\)H-NMR and \(^{13}\)C-NMR spectral data (DMSO-d\(_6\), \(\delta\) in ppm) confirmed the above results (Figs. 2, 3). The compound (Vc) was selected as a representative for this series, and showed the following significant \(^1\)H-NMR chemical shifts Fig. (4):
Two singlet at 2.32 and 2.34, each for 3H for the two (CH$_3$) protons, six peaks for the nine aromatic protons: multiplet at 7.12-7.28 for 3H (H-2', H-5', H-6'), triplet at 7.54 for 1H (H = N), doublet at 7.64 for 1H (J=7 Hz) (H-3), singlet at 7.70 for 1H (CH = N), multiplet at 7.85-7.89 for 2H (NH, H-7), multiplet at 8.48-8.53 for 2H (H-6, H-9), doublet at 8.90 for 1H (J=7) (H-2). The mass spectrum for compound Vc Fig. (5) showed the possible following fragmentation pattern (m/z) with the relative abundance of the fragments (%) as shown in Scheme (3).

Scheme 3: Fragmentation pattern of compound (Vc)
Table 3: Spectral data for compounds Va-j

| Compd. No. | IR (KBr) ν(cm⁻¹) | ¹H- NMR & ¹³C- NMR (DMSO-d₆) δ ppm |
|------------|------------------|-----------------------------------|
| Va         | C=C 1604         | 2.40 (s, 3H, CH₃), 7.25 (m, 4H, ArH), 7.53 (t, 1H, J=7Hz), 7.62 (d, 1H, J=7.5 Hz), 7.7 (s, 1H), 7.82-7.88 (m, 2H), 8.47-8.52 (m, 2H), 8.88(d, 1H, 7.5 Hz). |
|            | C=N 1647         |                                   |
|            | C=O 1685         |                                   |
|            | NH 3422          |                                   |
| Vb         | C=C 1605         | 2.37 (s, 3H, CH₃), 7.18-7.20 (m, 3H), 7.36 (m, 1H), 7.56(m, 2H), 7.83-7.95 (m, 3H), 8.34 (m, 1H), 8.81 (s,2H). |
|            | C=N 1649         |                                   |
|            | C=O 1682         |                                   |
|            | NH 3417          |                                   |
| Vc         | C=C 1608         | 2.32 (s, 3H, CH₃),2.34 (s. 3H, CH₃), 7.12-7.28 (m, 3H),7.54 (t, 1H), 7.64 (d,1H, J=7Hz), 7.70 (s,1H), 7.85-7.89 (m, 2H) 8.48-8.53 (m, 2H), 8.90 (d, 1H, J=7Hz). |
|            | C=N 1647         |                                   |
|            | C=O 1691         |                                   |
|            | NH 3473          |                                   |
| Vd         | C=C 1606         | 7.24-8.28 (m, 8H), 8.75-10.19 (m, 4H). |
|            | C=N 1647         | 111.22, 112.80, 116.47, 116.88, 126.19, 126.48, 126.85, 126.95, 127.23, 127.56, 127.91, 128.67, 134.23, 135.70, 136.82, 147.38, 148.44, 158.52, 165.49 |
|            | C=O 1695         |                                   |
|            | NH 3419          |                                   |
| Ve         | C=C 1603         | 4.36 (br,2H,NH₂), 6.37-7.11(m,7H), 7.30(m, 1H), 7.48-7.67 (m,3H),8.49(m,1H). |
|            | C=N 1647         | 102.06, 112.52, 114.93,115.89, 116.46, 117.74, 123.54, 124.95, 126.18, 127.02,127.17, 127.44, 127.69, 128.23, 135.37, 144.52, 146.90, 147.86, 158.70, 164.70 |
|            | C=O 1685         |                                   |
|            | NH 3443          |                                   |
| Vf         | C=C 1600         |                                   |
|            | C=N 1645         |                                   |
|            | C=O 1684         |                                   |
|            | NH 3422-3260     |                                   |
| Vg         | C=C 1605         |                                   |
|            | C=N 1645         |                                   |
|            | C=O 1685         |                                   |
|            | NH 3422          |                                   |
| Vh         | C=C 1606         |                                   |
|            | C=N 1646         |                                   |
|            | C=O 1684         |                                   |
|            | NH 3418          |                                   |
| Vi         | C=C 1604         | 0.85 (s,3H), 1.27 (s,4H), 1.54 (s, 2H), 2.38-2.86(m,2H), 7.37-7.49(br,2H), 7.74-7.88 (m, 3H), 8.09-8.29 (m, 2H), 8.45-8.73 (m, 1H). |
|            | C=N 1647         | 14.41, 22.11, 27.25, 29.43, 30.42, 114.43, 116.48, 125.04, 125.30, 125.93, 127.16, 127.25, 128.24, 135.32, 135.61, 148.63, 158.63, 164.87 |
|            | C=O 1684         |                                   |
|            | NH 3430          |                                   |
| Vj         | C=C 1607         | 2.9 (s, 2H, NH₂), 7.04 (d, 1H, J=4.5 Hz), 7.24 (t, 2H, J=7Hz),7.58-7.73 (m, 3H), 8.05 (d, 1H, J=7Hz) 8.39 (d, 1H, J=4.5 Hz). 114.42, 117.64, 120.88, 121.96, 122.32, 126.50, 134.12, 140.52, 146.83, 152.17, 152.61, 153.50, 179.30 |
|            | C=N 1645         |                                   |
|            | C=O 1683         |                                   |
|            | NH, NH₂ 3417-3255|                                   |
Compound IV has been prepared through the chlorination of compound II with excess SOCl₂ (Al-Hadedi, 2008; Al-Hadedi, 2009) as illustrated in Scheme (1). The structure of the synthesized compound IV was confirmed by means of physical data (m.p, R_f) and spectral data. The IR spectrum showed characteristic absorption peaks in the region (1649 cm\(^{-1}\)) for stretching of (C=N) bond, (1606 cm\(^{-1}\)) for stretching of (C=C) bond and there is absence of stretching band of (C=O) bond at (1695 cm\(^{-1}\)).

Compound VI has been prepared through the reaction of compound IV with hydrazine hydrate (Chandra et al., 2010; Al-Hadedi, 2009) as shown in Scheme (1). The structure of the synthesized compound VI was confirmed by means of physical data (m.p, R_f) and spectral data. The IR spectrum showed a characteristic broad absorption peaks in the region (3422-3314 cm\(^{-1}\)) which is due to the bond stretching of (NH, NH\(_2\)) bonds, 1649 cm\(^{-1}\) for stretching of (C=N) bond, and (1590 cm\(^{-1}\)) for stretching of (C=C) bond. The \(^1\)H-NMR and \(^13\)C-NMR spectral data for compound VI (Fig. 6) confirmed the above results and showed significant bands: singlet at 2.38 for 3H(CH\(_3\)), singlet at 2.75 for 2H (NH\(_2\)), broad band at 3.93-3.94 for 1H (NH). The chemical shifts of the aromatic protons are shown as following: doublet at 6.92 for 1H (J=7.2 Hz) (H-3), doublet at 7.68 for 1H (J=8 Hz) (H-8), multiplet at 7.84-7.89 for 2H (H-6, H-7), doublet at 8.26 for 1H (J=8Hz)(H-9), doublet at 8.69 for 1H(J=7.2 Hz)(H-2). The \(^13\)C-NMR for compound VI in (DMSO-d\(_6\)) \(\delta\) in ppm, showed the following chemical shifts: 20.78(CH\(_3\)), 115.38 (C\(_{4a}\)), 115.99 (C\(_{5a}\)), 123.04 (C\(_6\)), 124.48 (C\(_3\)), 124.68 (C\(_7\)), 126.52 (C\(_8\)), 126.66 (C\(_9\)), 134.43 (C\(_4\)), 146.43 (C\(_{9a}\)), 147.37 (C\(_5\)), 148.56 (C\(_2\)), 160.61 (C\(_{10a}\)).

The compounds VIIa-j have been prepared through the condensation of compound VI with various aromatic aldehydes (Chilin et al., 2002; Manoj and prasad., 2011) as illustrated in Scheme (1). The structure of the prepared compounds was elucidated by means of physical data (Table 2) (m.p, R_f) and spectral data (Table 4). The IR spectra of compounds VIIa-j showed a characteristic absorption bands at (3340-3300 cm\(^{-1}\)) for stretching of (N-H) band, (1625-1635 cm\(^{-1}\)) for stretching of (C=N) bond. The \(^1\)H-NMR spectrum for compound VIIb confirmed the structure of these compounds. The mass spectrum for compound VIIg showed the possible following fragmentation (m/z) with relative abundance (%) as shown in Scheme (4).
Scheme 4: Fragmentation pattern of compound (VIIg)
Table 4: Spectral data for compounds VIIa-j

| Compd. No. | IR (KBr), ν(cm⁻¹) | ¹H-NMR (DMSO-d₆) δ ppm |
|------------|-------------------|------------------------|
| VIIa       | C=C 1600          |                        |
|            | C=N 1624          |                        |
|            | NH 4430-3310      |                        |
| VIIb       | C=C 1602          | 2.36 (s, 3H,CH₃), 2.39 (s, 3H, CH₃), 7.32 (m, 5H), 7.77 (m, 3H), 8.66 (m, 2H). |
|            | C=N 1625          |                        |
|            | NH 3440-3300      |                        |
| VIIc       | C=C 1601          | 2.54 (s, 3H, CH₃), 6.97-7.01 (m, 4H), 7.40-7.42 (m, 2H), 7.70-7.72 (m, 2H), 9.00-9.05 (m, 3H), 11.1 (s, 1H). |
|            | C=N 1625          |                        |
|            | NH 3566-3421      |                        |
| VIIId      | C=C 1605          |                        |
|            | C=N 1625          |                        |
|            | NH 3430-3310      |                        |
| VIIe       | C=C 1595          |                        |
|            | C=N 1635          |                        |
|            | NH 3435-3325      |                        |
| VIIf       | C=C 1597          |                        |
|            | C=N 1635          |                        |
|            | NH 3340-3360      |                        |
| VIIg       | C=C 1602          |                        |
|            | C=N 1630          |                        |
|            | NH 3430-3340      |                        |
| VIIh       | C=C 1598          | 2.54 (s, 3H, CH₃), 3.82 (s, 3H, OCH₃), 7.05 (m, 6H), 7.08 (m, 4H), 8.63 (m, 2H). |
|            | C=N 1628          |                        |
|            | NH 3435-3340      |                        |
| VIIi       | C=C 1600          |                        |
|            | C=N 1625          |                        |
|            | NH 3360-3410      |                        |
| VIIj       | C=C 1602          | 2.54 (s, 3H, CH₃), 6.93-8.40 (m, 15H). |
|            | C=N 1630          |                        |
|            | NH 3435-3340      |                        |
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Fig. 1: Mass spectrum for compound (III)

Fig. 2: $^1$H-NMR spectrum for compound (VI)

Fig. 3: $^{13}$C-NMR spectrum for compound (VI)
Fig. 4: $^1$H-NMR spectrum for compound (Vc)

Fig. 5: Mass spectrum for compound (Vc)

Fig. 6: $^1$H-NMR spectrum for compound (VI)
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