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Synthetic and Spectral Studies of Novel Spiro {Bicyclo[3,3,0]octene-8,3′(2′H)-indol}-2′-ones Obtained from Indol-2,3-diones

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ABSTRACT: *The present article reports our approach toward the synthesis of spiro compounds via indol-2,3-diones. Thus, reaction of indol-2,3-dione derivatives with a secondary cyclic amino acid, namely, (R)-(−)-thiazolidine-4-carboxylic acid, affords a thiazolo-oxazolidinone as the main product. When the reaction is carried out in the presence of a dipolarophile, 1,3-dipolar cycloaddition to the intermediate azomethine ylide leads to a novel spiro compound. The products have been characterized on the basis of spectral studies, and the geometry of the intermediate iminium compound has been optimized by use of the semiempirical molecular orbital method.* © 1999 John Wiley & Sons, Inc. Heteroatom Chem 10: 381–384, 1999

INTRODUCTION

The importance attributed to the chemistry of indol-2,3-dione derivatives stems from their wide spectrum of biological activities [1–3] and their versatility toward a number of organic reactions. We have recently reported the reaction of indol-2,3-dione with pyrazolone derivatives furnishing bioactive spiro and nonspiro products [4,5]. In continuation of the aforementioned work, an attempt has been made to synthesize potent bioactive systems by reacting indol-2,3-dione with other five-membered heterocycles. For the present studies, the thiazolidine nucleus has been chosen because it is well recognized for its anti-inflammatory and antihypertensive activities [6,7], and therefore, a molecule incorporating these two moieties might be expected to be an effective biomolecule.

Refluxing equimolar amounts of isatin derivatives **1** with a secondary cyclic amino acid, that is, (R)-(−)-thiazolidine-4-carboxylic acid, **2**, in dry acetonitrile for 22 hours afforded compounds (2S, 5R)-spiro[1-aza-3-oxa-7-thia-bicyclo[3,3,0] octane-2,3′(2H)-indol]-4,2′-dione **4** in 40–53% yield. The configuration at C_2 and C_5 is in analogy with the previously assigned configuration of the [3,3,0]bicyclic N,O-acetal obtained by condensation of proline with pivaldehyde, as reported by Seebach et al. [8]. In contrast to our expectation for the reaction to occur at the active methylene site of the secondary amino acid, similar to that reported in the case of the reaction of isatin with pyrazolone affording spiro and nonspiro products, the present reaction occurs probably via the formation of the intermediate iminium species **3**. This is in conformity with a recent observation by Ardill et al. [9] for the reaction of carbonyl compounds with amines. The geometry of the iminium species has been optimized by the Semiempirical MOPAC 6.0 method using the AM1 Programme [10], and it appears that this species is stabilized by

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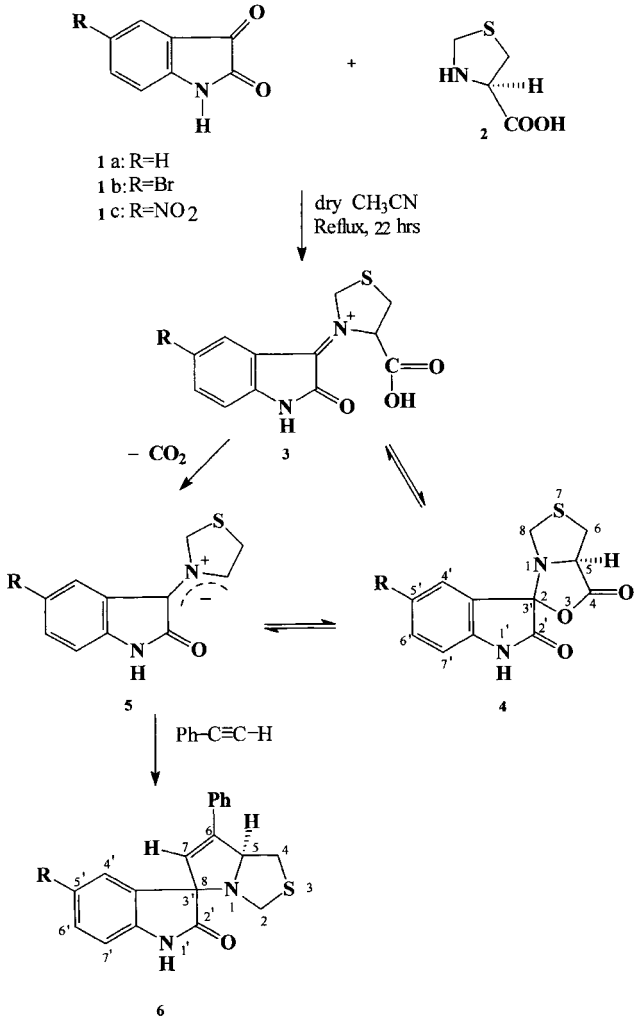

SCHEME 1

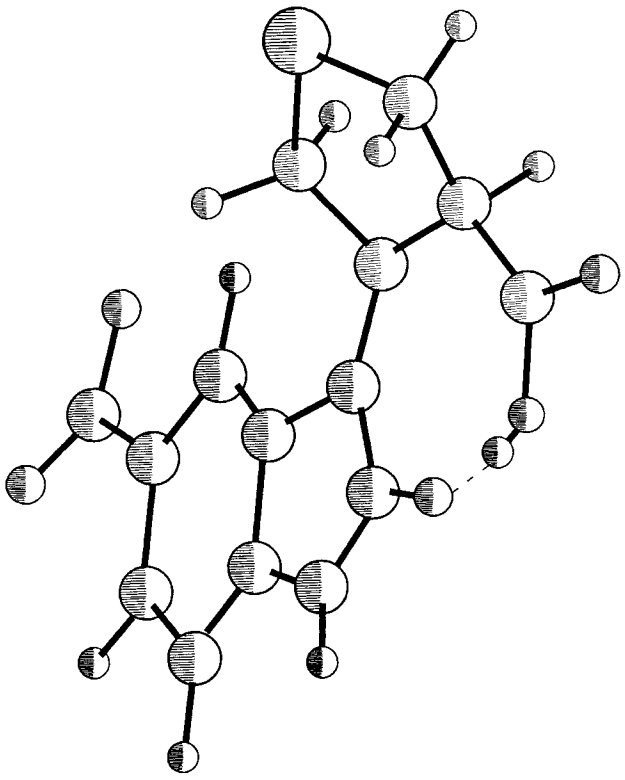

FIGURE 1 Semiempirical AM1 optimized geometry of iminium species **3c**.

H bonding between the carboxyl hydrogen and the keto group of isatin (Figure 1).

When the reaction of **1a** with **2** was carried out in the presence of a dipolarophile, for example, phenylacetylene, it led to the regiospecific formation of a novel spiro compound, (5S, 8S)-spiro{6-phenyl-1-aza-3-thia-6-bicyclo[3,3,0] octene-8, 3′(2′H)-indol}-2′-one **6a** in 50% yield. Once again, the assigned configuration at C_5, C_8 is in conformity with the configuration of the spiro-indol product obtained by the reaction of isatin with methyl acrylate and pyrrolidine [9]. Similar results were obtained by use of **1b** and **1c** instead of **1a**. The mechanism may involve the formation of an intermediate azomethine ylide **5**, formed during the reaction by the loss of CO_2, via a stereospecific 1,3-cycloreversion [11]. It subsequently undergoes 1,3-dipolar cycloaddition with phenylacetylene giving regiospecifically spiro compound **6**. Thus, it may be concluded that, in the absence of a dipolarophile, the iminium species **3** cyclizes to give **4**, whereas in the presence of a dipolarophile, it undergoes loss of CO_2 followed by 1,3-dipolar cycloaddition to give spiro compound **6**.

Structures of compounds **4** and **6** have been unambiguously established by their spectral data. In the IR spectra of **4a**, characteristic absorption bands were observed at 3350–3180 and 1780 cm^{-1} assignable to the -NH and lactone group, whereas the carbonyl peak was found at 1670 cm^{-1}. ^1H NMR spectra showed signals, corresponding to methylene protons as a multiplet at δ 2.95–3.39 (2×7′H) as well as at 3.76 (1 × 7a′H) and as singlet at 4.21 (2×5′H). Aromatic protons were seen as multiplets at δ 7.2 (ArH) and 7.6 (ArH). In addition, a singlet at δ 9.5 was associated with the imino protons. Compound **6** showed characteristic absorption due to a secondary amide at 3250 cm^{-1} and a ν_{CO} stretching band at 1680 cm^{-1}. In the ^1H NMR spectra, a multiplet centered around δ 2.9 and 3.4 was assigned to the CH_2 protons at position 1′, and a broad singlet corresponding to the olefinic C-6 proton was seen at δ 6.6. Aromatic protons were present as multiplets δ 6.9–7.1, 7.28, and 7.65. Moreover, the imino proton was found at δ 9.2 as a singlet. Additional evidence has been obtained by recording ^{13}C NMR spectra. Thus the ^{13}C

NMR spectrum of **6a**, as a typical case, showed the C-2′ carbonyl carbon at δ 180.6, whereas the spiro carbon C-8 was observed at δ 110.9. The olefinic carbons C-6 and C-7 were seen at δ 78.6 and 77.2, the chiral carbon C-5 appearing at δ 75.7, and the methylene carbons C-2 and C-4 were associated with δ 74.8 and 55.0. The remaining benzenoid carbons appeared in the region δ 141.7–112.9. The assigned values are in good agreement with literature data [12]. All these products were further confirmed by elemental analysis.

EXPERIMENTAL

All the operations were carried out under a nitrogen atmosphere. Melting points were determined in an open glass capillary tube and are uncorrected. The IR spectra were recorded on a Nicolet Magna IR™ spectrometer model 550 in KBr pellets. The ^{1}H NMR spectra were obtained on a Jeol FX-90Q model at 89.55 MHz with TMS as internal standard. Chemical shifts are given in δ. Elemental analyses were performed by use of a Perkin Elmer series C, H, N, S analyzer-2400. Acetonitrile was dried by refluxing with calcium chloride (anhydrous) for 5 to 6 hours and then distilling it. Phenylacetylene was obtained from Aldrich. Molecular modeling was performed by use of a PH4 PC model, Serena software (Bloomington, Indiana). Semiempirical calculations were performed on a PCL-Pentium P5 Computer using MOPAC 6.0. (R)-(−)-thiazolidine-4-carboxylicacid was purchased from Fluka.

Synthesis of (*2S, 5R*)-*Spiro{1-aza-3-oxa-7-thia-bicyclo[3,3,0]octane-2,3′*(*2H*)-*indol}-4,2′-dione* **4a**

A mixture of (R)-(−) thiazolidine-4-carboxylic acid (0.44 g, 3.3 mmol) and isatin (0.49 g, 3.3 mmol) in dry acetonitrile (50 mL) was refluxed under a nitrogen atmosphere for 22 hours. After completion of the reaction as monitored by thin-layer chromatography (TLC), unreacted thiazolidinecarboxylic acid **2** was filtered off from the cooled reaction mixture, and the filterate was evaporated to half its volume in vacuo. The concentrated reaction mixture was then allowed to stand. However, no crystals appeared after 15 hours, and therefore, the crude product was subjected to column chromatography over silica gel by elution with solvents of rising polarity.

Compound **4a** was obtained as orange crystals (0.30 g, 53%) from a benzene–ethyl acetate (4:1) fraction m.p. 145°(dec.). Calculated (found): C, 55.12 (55.17); H, 3.78 (3.83); N, 10.67 (10.72); S, 12.20 (12.26)%; ν_{max}(KBr): 3345–3370, 1770s, 1660s, 1500m, 1390, 1140 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$); δ 2.89–3.35 (m, 2 × 7′H), 3.74 (m, 7a′H), 4.20 (bs, 2 × 5′H), 7.16 (m, 2ArH), 7.45 (m, 2ArH), 9.3 (s, -NH).

Synthesis of (*2S, 5R*)-*Spiro{1-aza-3-oxa-7-thia-bicyclo[3,3,0]octane3,3′*(*2H*)-*5′-bromo-indol}-4,2′-dione* **4b**

Compound **4b** was obtained as orange crystals (0.14 g, 40%) from a benzene–ethyl acetate (4:1) fraction m.p. 135°(dec.). Calculated (found): C, 42.2 (41.8); H, 2.6 (2.4); S, 9.4 (9.1); N, 8.2 (7.9)%; ν_{max}(KBr): 3350–3180, 1780s, 1670s, 1500m, 1410, 1140 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$): δ 2.95–3.39 (m, 2 × 7′H), 3.76 (m, 7a′H), 4.21 (bs, 2 × 5′H), 7.2 (m, 2ArH), 7.6 (m, 1 ArH), 9.5 (s, -NH).

Synthesis of (*2S, 5R*)-*Spiro{1-aza-3-oxa-7-thia-bicyclo[3,3,0]octane-3,3′*(*2H*)-*5′nitro-indol}-4,2′-dione* **4c**

Obtained as an orangish-brown solid (0.20 g, 45%) from benzene–ethyl acetate (4:1). Calculated (found): C, 46.9 (46.3); H, 2.9 (2.6); N, 13.6 (13.2); S, 10.4 (10.1)%; ν_{max}(KBr): 3350–3200, 1775s, 1680s, 1500m cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz): δ 3.1–3.35 (m, 2 × 7′H), 3.85 (m, 1 × 7′aH), 4.5 (s; 2 × 5′H), 7.44 (m, 2ArH), 8.1 (m, 1ArH), 9.6 (s, -NH).

Synthesis of (*5S, 8S*)-*Spiro{6-phenyl-1-aza-3-oxa-7-thia-bicyclo[3,3,0]octene-8,3′*(*2′H*)-*indol}-2′-one* **6a**

A mixture of isatin (0.492 g, 3.3 mmol), (R)-(−)-thiazolidine-4-carboxylic acid (0.44 g, 3.3 mmol) and phenylacetylene (0.32 g, 3.1 mmol) was refluxed in acetonitrile (50 mL) for 22 hours. After the usual workup, that is, filtration of the unreacted thiazolidinecarboxylic acid and purification by column chromatography, compound **6a** was obtained as the first fraction on elution with benzene–ethyl acetate solvent.

Compound **6a** was obtained as orangish crystals (0.32, 50%) from benzene–ethyl acetate (7:1), m.p. 145°. Calculated (found): C, 71.21 (71.25); H, 4.64 (4.68); N, 8.72 (8.75); S, 9.6 (10.0)%, ν_{max}(KBr): 3245, 1670, 1600s, 1245, 1020m cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 2.75–3.3 (m, 2 × 1′H), 3.65 (m, 7a′H), 4.0 (s, 2 × 3′H), 6.45 (s, 7′H), 6.7–7.0 (m, 5ArH), 7.18 (m, 2ArH), 7.48 (m, 2ArH), 9.1 (s, -NH). ^{13}C NMR: δ 180.6 (C-2′), 141.8, 138.6, 130.5, 130.0, 128.6, 128.3, 127.7, 126.4, 125.6, 123.8, 122.9, 112.9 (12 benzenoid C), 110.9 (C-8), 78.6 (C-6), 77.2 (C-7), 75.7 (C-5), 74.2 (C-2), 55.0 (C-4).

Synthesis of (*5S, 8S*)-*Spiro{6-phenyl-1-aza-3-thia-6-bicyclo[3,3,0] octene-8,3′*(*2′H*)-*5′-bromo-indol}-2′-one* **6b**

A mixture of 5-bromoisatin (0.812 g, 3.35 mmol), (R)-(−)-thiazolidine-4-carboxylic acid (0.44 g, 3.3

mmol) and phenylacetylene (0.32 g, 3.1 mmol) was refluxed in acetonitrile (50 mL) for 22 hours, and after the usual workup, compound **6b** was obtained as orangish-brown crystals (0.16, 35%) from benzene–ethyl acetate (9:1), m.p. 150°. Calculated (found): C, 57.10 (56.7); H, 3.80 (3.76); N, 7.0 (6.7); S, 8.0 (7.8)%; ν_{max} (KBr): 3250, 1680, 1600s, 1250, 1020m cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 2.9–3.4 (m, 2 × 1′H), 3.72 (m, 7a′H), 4.1 (s, 2 × 3′H), 6.6 (s, 7′H), 6.9–7.1 (m, 5ArH), 7.28 (m, 2ArH), 7.65 (m, 1ArH), 9.2 (s, -NH). ^{13}C NMR: δ 180.0 (C-2′), 140.6, 133.4, 132.3, 130.8, 130.5, 128.9, 128.7, 128.5, 128.4, 127.6, 126.3, 115.6 (12 benzenoid C), 112.2 (C-8), 78.6 (C-6), 77.1 (C-7), 75.7 (C-5), 74.8 (C-2), 55.1 (C-4).

Synthesis of (5S, 8S)-Spiro{6-phenyl-1-aza-3-thia-6-bicyclo[3,3,0]octene-8, 3′(2′H)-5′-nitro indol}-2′-one **6c**

Obtained as an orangish solid (0.18 g, 42%) from benzene–ethyl acetate (6:1). Calculated (found): C, 62.4 (61.9); H, 4.1 (3.7); N, 11.5 (11.2); S, 8.7 (8.3); ν_{max}(KBr): 3300, 1675, 1610, 1250, 1120 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 3.1–3.35 (m, 2 × 1′H), 3.72 (m, 7a′H), 4.4 (s, 2 × 3′H), 6.72 (s, 7′H), 6.98–7.2 (m, 5ArH), 7.35 (m, 2ArH), 7.72 (m, 1ArH), 9.4 (s, -NH).

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