SYNTHESIS OF POLYCYCLIC BISMESOIONIC COMPOUNDS

Chok Wah Lo,[1] Wing Lai Chan,*[1] Yau Shan Szeto,[2] and Chiu Wing Yip[1]

[1]Department of Applied Biology and Chemical Technology, [2]Institute of Textiles and Clothing, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong

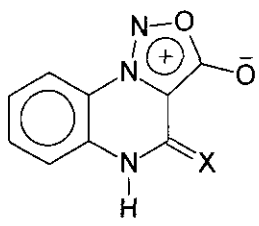
Abstract –Sydno[3,4-*a*][1,3]thiazolo[2,3-*c*]quinoxalin-6-one was synthesized from readily available sydno[3,4-*a*]quinoxalin-4-thione. In an attempted synthesis of sydnonyl-1,2,4-thiadiazol-3-one, an unexpected dimer bissydno[3,4-*a*]quinoxalin-4-yl disulfide was obtained.

INTRODUCTION

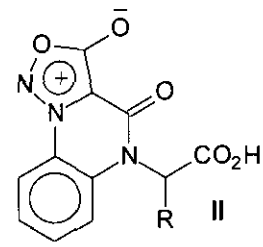
Mesoionic compounds have been extensively studied because of their unique structure and pharmaceutical properties.[1] A large number of monomesoioionic compounds are known, and a few fused ring and bismesoionic systems are also reported, but bismesoionic compounds with different mesoionic nuclei do not exist. We now report the synthesis of such a bismesoionic system.

RESULTS AND DISCUSSION

Since fused ring sydno[3,4-*a*]quinoxalin-4-one[2-4] (**Ia**) and -4-thione[4] (**Ib**) possess the essential functional parts, carbamoyl and thiocarbamoyl group, it was of interest to explore and utilize these groups to construct a second mesoionic ring oxazole and thiazole respectively on **Ia** and **Ib**. It was expected that the reactions of **Ia** with α-bromocarboxylic acid would give the amino acid (**II**), and **Ib** would react in a slightly different manner to give thioglycollic acid (**III**).



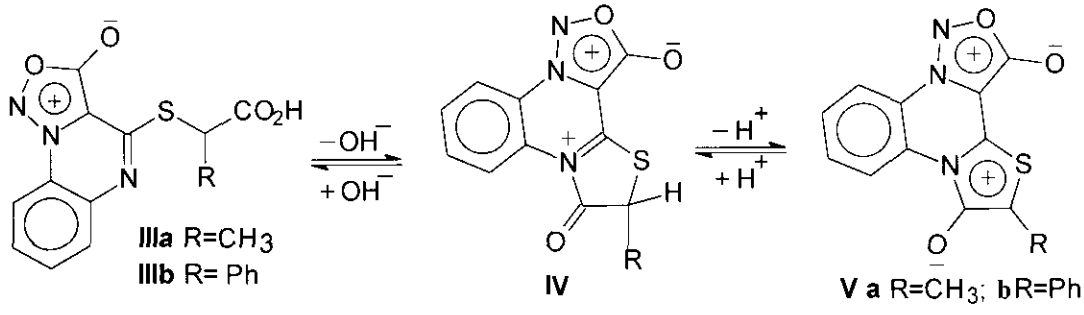
Ia X=O
Ib X=S



II

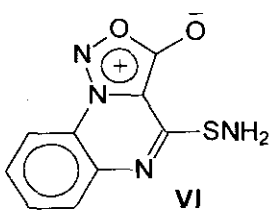
Various attempts to couple α-bromocarboxylic acid on quinoxalin-4-one were failed. On the other hand, the reaction of α-bromocarboxylic acid with **Ib** in refluxing THF in the presence of triethylamine occurred readily affording **III**. So, the reaction with α-bromopropionic acid gave α-sydno[3,4-*a*]-

quinoxalin-4-sulfanylpropionic acid (**IIIa**), and with α-bromophenylacetic acid yielded α-sydno[3,4-*a*]quinoxalin-4-sulfanylphenylacetic acid (**IIIb**). Treating **IIIa** with acetic anhydride, according to the general method established in the synthesis of 1,3-thiazol-4-one[5] in THF produced 5-methylsydno[3,4-*a*][1,3]thiazolo[2,3-*c*]quinoxalin-6-one (**Va**). Similarily, **IIIb** generated 5-phenylsydno[3,4-*a*][1,3]thiazolo[2,3-*c*]quinoxalin-6-one (**Vb**). The characteristic CO absorptions of the sydnone and thiazole rings of both compounds were clearly seen on IR spectra. All other spectroscopic analytical data agreed with the molecular structures. 1,3-Dipolar cycloaddition using dimethyl acetylenedicarboxylate for both compounds was unsuccessful. Under moderate conditions, no reaction was found and unreacted compounds were recovered, whereas in vigorous conditions, decompositions of **V** occurred. No other chemical reaction was performed on **V** successfully, except that **V** was easily hydrolyzed back to **III** in TFA solutions in the presence of water. The ^{1}H NMR spectrum of **Va** showed four aromatic protons (δ 9.43-8.06), and three methyl protons at δ 2.98 as a doublet(J=7 Hz). One unexpected proton was found at δ 4.97 as quartet (J=7 Hz). This indicated that **Va** in TFA solution existed as **IV** (R=CH_3). The same situation was observed in **Vb**, the proton was found at δ 6.04 in a much smaller proportion. The hydrogen ratio was calculated as 0.3 : 9 using the nine aromatic protons as a reference. **Vb** only partially existed in the form as **IV** (R=Ph) in TFA solution, thus **Vb** was found more stable than **Va**, which decomposed quite fast in TFA solution.

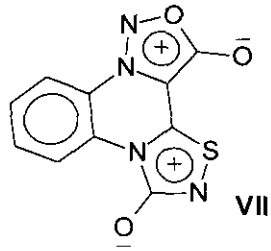


The success in the synthesis of **V** prompted us to synthesize the sydnonylthiadiazole (**VII**). It was anticipated that the introduction of amino group onto the sulfur atom of **Ib** would give sydno[3,4-*a*]quinoxalin-4-sulfanylamine (**VI**). Treating **VI** with phosgene or $CoIm_2$ would lead to the formation of **VII**. **VI** was smoothly prepared from **Ib** using hydroxylamine-*O*-sulfonic acid (HOSA). However attempts to prepare **VII** by reacting **VI** with various reagents such as phosgene, thiophosgene, 1,1'-carbonyldiimidazole, and 1,1'-thiocarbonyldiimidazole were all unsuccessful. Surprisingly, all reactions yielded identical products. The ^{1}H NMR spectrum of the compound indicated the *ortho* substituted benzene ring protons, the IR spectrum showed the CO absorption of the sydnone ring, and the CNH elemental analysis suggested the empirical formula of the compound was $(C_9H_4N_3O_2S)_n$. Notwithstanding the lack of the support of MS data, which were unable to obtain for this compound, all

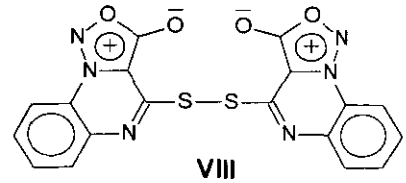
available data suggested that this compound was a dimer. No other reaction mechanism was able to be drawn that all the four different reactions could lead to the formation of the same product using different reagents mentioned, except *via* a free radical reaction. It must be the homolysis of the S-NCX bond and formed thiyl radicals, which coupled themselves and gave the bissydno[3,4-*a*]quinoxalin-4-yl disulphide (**VIII**).



VI



VII



VIII

EXPERIMENTAL

α-Sydno[3,4-*a*]quinoxalin-4-sulfanylpropionic acid (IIIa)

A mixture of sydno[3,4-*a*]quinoxalin-4-thione (**Ib**) (0.6 g, 3 mmol), α-bromopropionic acid (0.6 g, 4 mmol) and triethylamine (0.6 g) in THF (10 mL) was refluxed for 2 h. The mixture was then cooled and poured into water (50 mL). The resulting mixture was acidified to pH 6 with 0.7 % hydrochloric acid. The solid formed was filtered and washed three times with water (3x10 mL). The product was recrystallized from ethanol to give yellow crystals of **IIIa** (0.98 g, 92%),mp 194-195 °C(decomp); IR (KBr)1759s, 1704s, 1574m, 1513s, 1499s, 1443s, 1426m, 1377w, 1307m, 1237m, 1212s, 1085w, 985s, 924w, 772s cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) δ 8.31-8.33 (m, 1H), 7.94-7.96 (m, 2H), 7.74-7.78 (m, 1H), 4.88 (q, 1H; J=7.2 Hz), 1.70 (d, 3H; J=7.2 Hz). Anal. Calcd for $C_{12}H_9N_3O_4S$: C, 49.48; H, 3.11; N, 14.42; MS m/z 291.0314. Found: C, 49.05; H, 3:30; N, 14.22; MS (ESI) (m+1)/z 292.0397.

α-Sydno[3,4-*a*]quinoxalin-4-sulfanylphenylacetic acid (IIIb)

Similarly **IIIb** was prepared using α-bromophenylacetic acid, the product obtained was recrystallized from ethanol to afford pale yellow crystals (95% yield),mp 197-198 °C(decomp); IR (KBr) 1813m, 1775s, 1717m, 1604w, 1575m, 1512s, 1495s, 1444s, 1421m, 1401w, 1376m, 1302w, 1189w, 1152w, 1110w, 1077w, 1029w, 976s, 931w, 880w, 834w, 758s, 719s cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) δ 8.31-7.38 (m, 9H), 5.94 (s, 1H). Anal. Calcd for $C_{17}H_{11}N_3O_4S$: C, 57.78; H, 3.14; N, 11.89; MS m/z 353.0470. Found: C, 57.80; H, 3.00; N, 11.55; MS (ESI) (m+1)/z 354.0394.

5-Methylsydno[3,4-*a*][1,3]thiazolo[2,3-*c*]quinoxalin-6-one (Va)

A mixture of acetic anhydride (0.3 g, 1.5 mmol) and **IIIa** (0.2g, 0.7 mmol) was stirred in dry THF (10 mL) at 0 °C for 1 h and a further 3 h at rt. The precipitate was collected and washed with THF (2x1 mL). Dark blue crystals of **Va** (0.11g, 58.7%) were obtained after recrystallization from THF, mp 183-184 °C (decomp); IR (KBr) 1766s, 1747s, 1722m, 1621s, 1604s, 1488s, 1463m, 1330w, 1291w, 1151w, 1123w, 1112m, 978m, 877m, 774m cm^{-1}; ^1H NMR (TFA, 400 MHz) δ 9.42 (d, 1H; J=8 Hz), 8.62 (d, 1H; J=8 Hz), 8.25 (t, 1H; J=8 Hz), 8.08 (t, 1H; J=8 Hz), 4.97 (q, 1H, J=7 Hz), 2.10 (d, 3H; J=7 Hz); Anal. Calcd for $C_{12}H_7N_3O_3S$: MS m/z 273.0208. Found: MS (ESI) (m+1)/z 274.0361.

5-Phenylsydno[3,4-*a*][1,3]thiazolo[2,3-*c*]quinoxalin-6-one (Vb)

Similarly **Vb** was prepared from **IIIa**, the precipitate collected was recrystallized from DMF and yielded dark blue crystals of **Vb**, (82% yield), mp 251-252 °C (decomp); IR (KBr): 1778s, 1761s, 1633s, 1600m, 1489s, 1468s, 1450m, 1433w, 1383m, 1350m, 1330m, 1120s cm^{-1}; ^1H NMR (TFA, 400 MHz) δ 9.5-8.7 (m, 9H), 6.1 (s, 0.3H); Anal. Calcd for $C_{17}H_9N_3O_3S$: C, 60.89; H, 2.70; N, 12.57; MS m/z 335.0380. Found: C, 60.52; H, 2.40; N, 12.22; MS (ESI) (m+1)/z 336.0606.

Sydno[3,4-*a*]quinoxalin-4-sulfanylamine (VI)

Sydno[3,4-*a*]quinoxalin-4-thione (1.0 g, 4.6 mmol) was suspended in sodium hydroxide solution (0.65 M, 40 mL) at rt with stirring, to which HOSA (1.0 g, 8.8 mmol) was added in small portions. After addition was completed, the mixture was allowed to stand for 48 h. The precipitate collected was washed with water (20 mL) and recrystallized from ethanol to afford **VI** (0.65 g, 60%) as white leaflets, mp 256-258 °C (decomp); IR (KBr): 3380w, 3290w, 1810w, 1700s, 1570m, 1475m, 1300w, 1110w, 990w, 975m, 880m, 775m, 720m cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 7.5-8.3 (m, 4H), 4.15 (s, 2H); Anal. Calcd for $C_9H_6N_4O_2S$: C, 46.14; H, 2.58; N, 23.92; MS m/z 234. Found: C, 46.32; H, 2.62; N, 23.83; MS m/z 234.

Bissydno[3,4-*a*]quinoxalin-4-yl disulfide (VIII)

1.) **VI** (0.2 g, 0.85 mmol) was added to a solution of thiophosgene (0.1 g, 0.92 mmol) or phosgene (0.09 g, 0.9 mmol) in chloroform (25 mL), in the presence of excess amount of potassium carbonate (2.0 g, 14.5 mmol) at 0 °C with stirring. The mixture was kept at 0 °C for 1 h and then refluxed for 1 h. The contents were filtered and the residue was treated with a large amount of water, to yield a white powder (56% for thiophosgene and 68% for phosgene) after drying.

2.) A mixture of **VI** (0.2 g, 0.85 mmol) and 1,1'-carbonyldiimidazole (0.15 g, 0.92 mmol) or 1,1'-thiocarbonyldiimidazole (0.16 g, 0.9 mmol) in dry toluene (15 mL) was gently refluxed for 3 h, and the precipitates were collected and washed with a small amount of THF to give a white powder (over 80% yield for both carbonyl and thiocarbonyldiimidazole).

White crystals were obtained after recrystallization from DMSO, mp 280 °C (decomp); IR (KBr): 3077w, 1808w, 1751s, 1574m, 1520m,1494s, 1443s, 1308m,1125w, 983m, 971s, 858m, 777s cm^{-1}; ^1H NMR (TFA, 400 MHz) δ 8.58(d, 1H; J=8.0 Hz), 8.25(d, 1H; J=8.0 Hz), 8.17(dd, 1H; J=8.0, 7.8 Hz), 8.06(dd, 1H; J=8.0, 7.8 Hz); Anal. Calcd for $C_{18}H_8N_6O_4S_2$: C, 49.54; H, 1.85; N, 19.26. Found: C, 49.38; H, 1.91; N, 19.20.

REFERENCES

1. a.) M. Ohta and H. Kato, 'Non-benzenoid Aromatics', ed. by J. P. Snyder, Academic Press, New York, 1969, p. 117; b.) W. D. Ollis and C. A. Ramsden, 'Advanced Heterocyclic Chemistry,' ed. by A. R. Katritzky and A. J. Boulton, Academic, New York, 1976, **19**, 1; c.) C. G. Newton and C. A. Ramsden, Tetrahedron, 1982, **38**, 2965; d.) K. T. Potts, '1,3-Dipolar Cycloaddition Chemistry', ed. by A. Padwa, Wiley, New York, 1984, **2**, 1; e.) K. T. Potts, J. Baum, E. Houghton, D. N. Roy, and U. P. Singh, J. Org. Chem., 1974, **39**, 3916; f.) L. B. Kier and E. B. Roche, J. Pharm. Sci., 1967, **56**, 147.
2. R. A. Coburn and J. P. O'Donnell, J. Org. Chem., 1972, **37**, 1707.
3. P. N. Preston and K. Turnbull, J. Chem. Soc., Perkin Trans. 1, 1977, 1229.
4. W. L. Chan, J. A. Waite, Y. H. Lin, and Y. S. Szeto, Heterocycles, 1994, **9**, 2023.
5. K. P. Potts, U. P. Singh, and E. Houghton, Chem. Commun., 1969, 1128.

Received, 3rd February, 1999