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A FACILE SYNTHESIS OF NOVEL HETEROPOLYCYCLIC PYRAZINES AND OXAZOLES AND MECHANISTIC STUDIES OF 2,3-DIHYDROBENZO[*de*]CHROMENE-7,8-DIONE WITH AMINES

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Abstract – A series of novel heteropolycyclic pyrazines and oxazoles were synthesized by the reaction of 2,3-dihydrobenzo[*de*]chromene-7,8-dione (compound **1**) with amines in mild reaction conditions. The mechanisms for these reactions were discussed.

INTRODUCTION

Mansonone compounds represent a series of naturally occurring *o*-quinones. These compounds had shown comprehensive pharmacological activities such as antifungal,[1,2] antioxidation,[3] antibacterial[4-6] and antitumor activities.[7-8] In early research work, we designed and synthesized serial mansonone F derivatives, and there synthetic compounds showed the significant cytotoxic activity.[8] In this paper, we reported the reactions of compound **1** with amines which included mono-, di-, aromatic and aliphatic, resulting in constructing new heterocyclic systems, such as heteropolycyclic pyrazines and heteropolycyclic oxazoles.

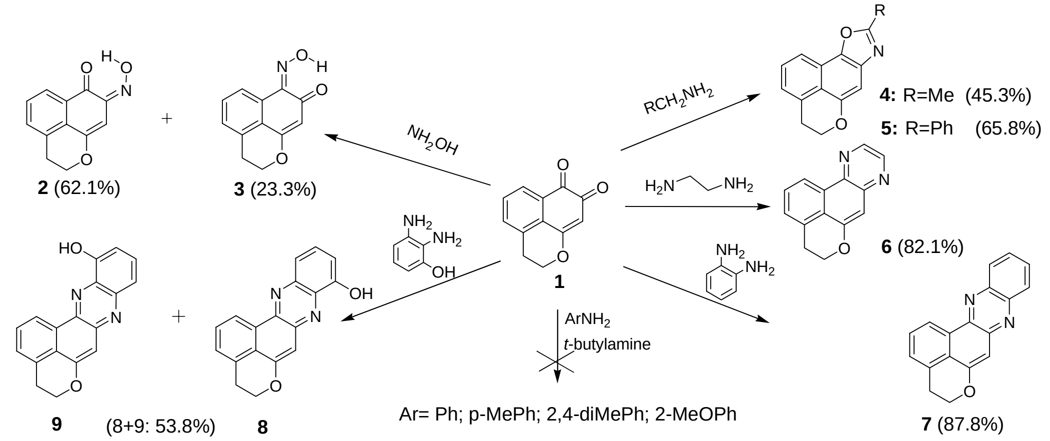
mansonone F **1**

Figure 1. The structure of mansonone F and compound **1**

RESULTS AND DISCUSSION

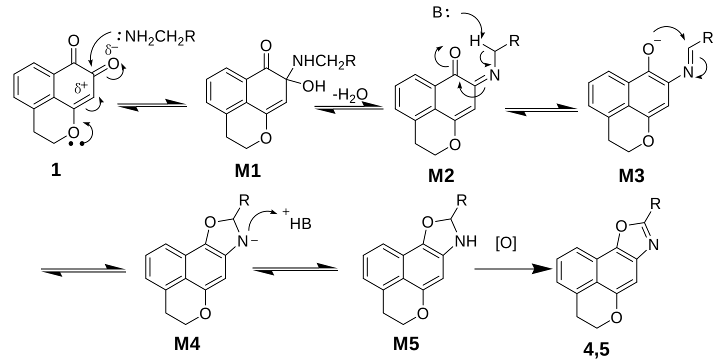
2,3-Dihydrobenzo[*de*]chromene-7,8-dione (compound **1**) was optimized the structure from mansonone F (shown as Figure 1). The cytotoxic activity of **1** compared favourably with camptothecin (data not shown).

The reaction of **1** with various amines gave different products (shown as Scheme 1).



Scheme 1. The reaction of compound **1** with amines

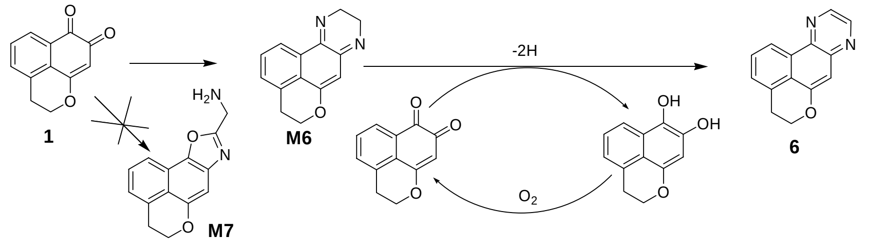
In general, imine was the main product for the reaction of primary amine with ketone. Unexpectedly, the reaction of **1** with primary amines contain α-methylene in the structure, such as ethylamine and benzylamine, could not give the imine products at room temperature even though adding large excess of amine. In mass spectrum, $[M+1]^+$ peak showed that the molecular weight was 2 less than that of corresponding imine. According to the ^1H NMR data, we found all of the proton in **1** and amine were remained except $N-CH_2-R$. For these reasons, we supposed that a two step reaction, condensation and oxidation were included, and the reaction would proceed only between 7,8-dione of **1** and NH_2CH_2-. Finally, the structures of **4** and **5** were determined as 9-methyl-4,5-dihydro-6,10-dioxa-8-aza-cyclopenta-[*a*]phenalene and 9-phenyl-4,5-dihydro-6,10-dioxa-8-aza-cyclopenta[*a*]phenalene according to the spectral data. In general, it was difficult to synthesize for these heterotetracyclic oxazole derivatives. The mechanism of reaction was supposed as shown in Scheme 2.



Scheme 2. Mechanism of the reaction of compound **1** with primary amines

In Scheme 2, the 8-carbonyl group was attacked more easily by nucleophilic reagent comparing with 7-carbonyl group, that due to the conjugating effect of carbonyl group at 7-position with benzene ring and the p-π conjugating effect of oxygen at 1-position. That's the reason why only the product of 8-carbonyl attacked was presented. The imine **M2**, the key intermediate, was tautomerized to phenolic anion **M3** with base catalyst, followed by intramolecular neucleophilic addition to produce **M5**. In oxidant present, intermediate **M5** transformed to more stable **4** and **5**.

The reaction of compound **1** with other amines without α-methylene, such as hydroxylamine, *t*-butylamine and arylamines, was also investigated. The reaction of compound **1** with hydroxylamine gave imine products **2** and **3**. The structures of **2** and **3** were assigned respectively as 2,3-dihydro-8-(hydroxyimino)benzo[*de*]chromen-7(8*H*)-one and 2,3-dihydro-7-(hydroxyimino)benzo[*de*]-chromen-8(7*H*)-one according to the ^{1}H NMR, ^{13}C NMR, HMBC, HMQC and MS. As already explained, compound **2** was the main product, the yield of **2** was two times more than that of **3**. It is due to the similar reason as above discussion that 8-carbonyl group has stronger electrophilicity. In addition, we found aromatic monoamine and *t*-butylamine have no any reaction with **1** even heating the reactants one day. We proposed that the reaction was difficult to carry out for the weaken basicity of arylamine and the bulky steric hindrance of *t*-butylamine.



Scheme 3. Mechanism of the reaction of compound **1** with 1,2-diaminoethane

When diamine was used instead of monoamine, the reaction of compound **1** with 1,2-diaminoethane could be carried out at room temperature. However, the corresponding oxazole derivative **M7** was not produced in the reaction though 1,2-diaminoethane contains α-methylene group. Instead, the quinoxaline derivative **6** was obtained with a high yield of 82.1 %. The reaction mechanism was proposed in Scheme 3. **M6** as an intermediate was oxidated to **6** by **1** in the reaction system and **1** was reduced to *o*-catechol, which was reoxidated easily to **1** by oxygen.

Furthermore, other novel pyrazine derivatives could be synthesized by this reaction. It had been reported that the reaction of *o*-aryldiamine with *o*-quinone was fast and complete.[9] Therefore, it is convenient to obtain the stable phenazine derivatives **7**, **8** and **9**. But we could not distinguish and isolate the isomers **8** and **9**, because the hydroxyl group at different position has no shown distinction in spectral data.

In conclusion, we had developed a convenient method to synthesize heteropolycyclic pyrazines and oxazoles in mild reaction conditions. The reaction of compound **1** with aliphatic amine contain α-methylene produced oxazoles. In the same reaction with diamine, the products were only pyrazines. The reaction of compound **1** with aliphatic amine without α-methylene would obtained the main 8-imine products. *t*-Butylamine and aromatic monoamine had no any reaction for the weaken basicity or the bulky steric hindrance. The reactivity of carbonyl group at 7- or 8-positions and the structure of amine were the key factors affecting the product and mechanism.

EXPERIMENTAL

Melting points were measured on a WRR melting-point apparatus (Shanghai Physical Optical Equipment Manufacturer) or SGW X-4 melting-point apparatus with microscope (Shanghai Physical Optical Equipment Manufacturer), and the thermometer was uncorrected. ^{1}H NMR and ^{13}C NMR were recorded on a Varian Inova 500NB or Mercury-Plus 300 NMR instrument with TMS as internal reference. Mass spectra were recorded on a Finnigan TSQ Quantum instrument. IR spectra were recorded on Bruker Equinox 55 Fourier transform spectrometer. Elemental analyses were performed by Elementar Vario EL instrument.

Starting Materials. Compound **1** was prepared by the appropriate reported procedures.[8] All other chemicals used in this study were commercially available.

(7*Z*)-2,3-Dihydro-7-(hydroxyimino)benzo[*de*]chromen-8(7*H*)-one (2) and (8*Z*)-2,3-dihydro-8-(hydroxylimino)benzo[*de*]chromen-7(8*H*)-one (3) : To a stirred suspension of compound **1** (100 mg, 0.5 mmol) in MeOH (15 mL) was added hydroxylamine hydrochloride (69.5 mg, 1 mmol) and anhydrous K_2CO_3 (415 mg, 3 mmol). The solution was stirred for 3 h at rt. The progress of the reaction was examined on TLC plate (30:1 $CHCl_3$-MeOH **2**: R_f=0.5, **3**: R_f=0.2). The resulting mixture was concentrated in vacuo. The crude product was washed with petroleum ether/ MeOH=1:1 and purified by silica gel column chromatography to give **2** and **3** (50:1 $CHCl_3$-MeOH).

Compound **2**: A yellow solid. Yield (25 mg, 23.2 %). mp 139.4~140.8 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.15（2H, t, *J* = 5.6 Hz）, 4.53 (2H, t, *J* = 5.6 Hz), 6.03 (1H, s), 7.29 (1H, d, *J* = 7.4 Hz), 7.52 (1H, t, *J* = 8 Hz), 8.19 (1H, d, *J* = 7.9 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 26.2, 67.4, 105.0, 120.9, 128.8, 130.6, 131.9, 133.8, 133.9, 143.5, 168.8; IR (KBr, cm^{-1}) ν_{max} 3459, 1636, 1594, 1532, 1198, 1098, 842, 772; ESI-MS: 215[M]$^+$; Anal. Calcd for $C_{12}H_9NO_3$: C, 66.97; H, 4.22; N, 6.51. Found: C, 67.05; H, 4.38; N, 6.35.

Compound **3**: A yellow solid. Yield (66.8 mg, 62.1 %). mp 207.5~209.1 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.04 (2H, t, *J* = 5.3 Hz), 4.30 (2H, t, *J* = 5.3 Hz), 6.37 (1H, s), 7.51 (1H, t, *J* = 7.4 Hz), 7.58 (1H, d, *J* = 7.0 Hz), 7.89 (1H, d, *J* = 7.1 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 27.6, 66.5, 95.6, 126.3, 127.9, 130.3, 131.4, 134.0 (2C), 134.7, 153.1 (2C); IR (KBr, cm^{-1}) ν_{max} 3414, 1685, 1628, 1569, 1205, 1122, 1020, 944, 829, 767; ESI-MS: 215[M]$^+$; Anal. Calcd for $C_{12}H_9NO_3$: C, 66.97; H, 4.22; N, 6.51. Found: C, 66.80; H, 4.15; N, 6.72.

9-Methyl-4,5-dihydro-6,10-dioxa-8-aza-cyclopenta[*a*]phenalene (4). Compound **4** was prepared from **1** according to the procedure for **2**. A pink viscous oil. Yield (51 mg, 45.3 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ

2.72 (3H, s), 3.26 (2H, t, *J* = 5.7 Hz), 4.42 (2H, t, *J* = 5.7 Hz), 7.20 (1H,s), 7.20 (1H, d, *J* = 7.0 Hz), 7.52 (1H, dd, *J* = 8.3, 7.0 Hz), 7.99 (1H, d, *J* = 8.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.7, 29.6, 66.3, 101.8, 118.2, 119.6, 119.8, 122.4, 126.8, 132.0, 138.1, 141.3, 150.7, 163.3; ESI-MS: 226[M+1]$^+$; Anal. Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.28; H, 5.25; N, 6.35.

9-Phenyl-4,5-dihydro-6,10-dioxa-8-aza-cyclopenta[*a*]phenalene (5). Compound **5** was prepared from **1** according to the procedure for **2**. A pale yellow solid. Yield 65.8 %. mp 176.7~180.1 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.28 (2H, t, *J* = 5.7 Hz), 4.45 (2H, t, *J* = 5.7 Hz), 7.23 (1H, d, *J* = 7.0 Hz), 7.31 (1H, s), 7.53 (3H, m), 7.57 (1H, dd, *J* = 7.0, 8.3 Hz), 8.12 (1H, d, *J* = 8.3 Hz), 8.31 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.5, 66.3, 102.0, 118.5, 120.0, 120.1, 122.7, 126.9, 127.2(2C), 127.5, 128.9(2C), 131.0, 132.0, 139.0, 141.3, 151.1, 162.7; IR (KBr, cm^{-1}) ν_{max} 1638, 1617, 1581, 1551, 1291, 1174, 1112, 1015, 767, 701; ESI-MS : 288[M+1]$^+$; Anal. Calcd for $C_{19}H_{13}NO_2$: C, 79.43; H, 4.56; N, 4.88. Found: C, 79.61; H, 4.43; N, 4.51.

4,5-Dihydroisochromeno[8,1-*fg*]quinoxaline (6). To a stirred suspension of compound **1** (250 mg, 1.25 mmol) in MeOH (40 mL) was added 1,2-diaminoethane (225 mg, 3.75 mmol) and the solution was stirred for 18 h at rt. The progress of the reaction was examined on TLC plate. The resulting mixture was concentrated to one-third of its original volume in reduced pressure. The remained liquid was cooled and filtrated. The crude product was purified by silica gel column chromatography to give **6**. A yellowish white solid. Yield (228 mg, 82.1 %). mp 114.6~116.0 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.36 (2H, t, *J* = 5.3 Hz), 4.54 (2H, t, *J* = 5.3 Hz), 7.35 (1H, s), 7.52 (1H, d, *J* = 6.8 Hz), 7.74 (1H, t, *J* = 8.0 Hz), 8.78 (2H, d, *J* = 15.5 Hz), 9.07 (1H, d, *J* = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.2, 66.6, 107.6, 123.3, 123.5, 127.1, 128.0, 131.1, 131.6, 138.4, 140.9, 144.5, 144.8, 155.1; IR (KBr, cm^{-1}) ν_{max} 1622, 1603, 1538, 1518, 1191, 1114, 848, 775, 766; ESI-MS: m/z 223[M+1]$^+$; Anal. Calcd for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.60. Found: C, 75.61; H, 4.85; N, 12.74.

4,5-Dihydroisochromeno[8,1-*ab*]phenazine (7). Compound 7 was prepared from **1** according to the procedure for **6**. A pale yellow solid. Yield 87.8 %. mp 192.2~194.1 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.34 (2H, t, *J* = 5.3 Hz), 4.56 (2H, t, *J* = 5.3 Hz), 7.34 (1H, s), 7.54 (1H, d, *J* = 7.5 Hz), 7.79 (3H, m), 8.20 (1H, d, *J* = 7.8), 8.30 (1H, d, *J* = 8.4), 9.25 (1H, d, 8.0); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.0, 66.6, 107.1, 124.3, 128.3, 128.6, 128.7, 128.9, 129.1, 129.9, 130.1, 131.5, 131.7, 140.4, 140.9, 143.3, 145.4, 156.2; IR (KBr, cm^{-1}) ν_{max} 1631, 1602, 1533, 1186, 1117, 853, 759; ESI-MS m/z 273[M+1]$^+$; Anal. Calcd for $C_{18}H_{12}N_2O$: C, 79.39; H, 4.44; N, 10.29. Found: C, 79.18; H, 4.35; N, 10.35.

4,5-Dihydroisochromeno[8,1-*ab*]phenazin-9-ol (8) and **4,5-dihydroisochromeno[8,1-*ab*]phenazin-12-ol (9).** Compound **8+9** was prepared from **1** according to the procedure for **6**. A yellow solid. Yield 53.8 %. mp 182~185 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.32 (2H, t, *J* = 5.3 Hz), 4.54 (2H, t, *J* = 5.3 Hz), 7.25 (2H, m), 7.52 (1H, d, *J* = 6.8 Hz), 7.70 (2H, m), 7.76 (1H, m, *J* = 8.3 Hz), 8.13 (1H, s, br), 9.20 (1H, d, *J* =

7.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.0, 66.7, 106.7, 109.6, 120.2, 124.3, 124.5, 128.5(2C), 129.6, 131.5, 131.7, 133.7, 141.1, 143.2, 147.8, 151.5, 156.2; IR (KBr, cm^{-1}) ν_{max} 1633, 1614, 1572, 1549, 1534, 1491, 1184, 1115, 849, 760, 738; ESI-MS: 289$[M+1]^+$; Anal. Calcd for $C_{18}H_{12}N_2O_2$: C, 74.99; H, 4.20; N, 9.72. Found: C, 75.15; H, 4.08; N, 9.55.

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