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Effect of Time in the Synthesis of an Intermediate of Phenothiazine Derivatives

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During the synthesis of a derivative from phenothiazine, two distinct competitive reactions were detected. In this paper, some proofs about these reactions were examined.

Key Words: Intermediate, Phenothiazine, Reversible-reaction.

INTRODUCTION

In pharmaceuticals industry, asymmetric phenothiazine derivatives were synthesized[1-7] for manufacturing anticonvulsants, antifungals, antibacterials. Symmetric phenothiazine derivatives were reported rarely. For this reason, a series of symmetric phenothiazine derivatives were designed for getting some novel biological activities such as 3,7-disubstituted 10-ethyl phenothiazine. An intermediate was prepared by special method because of two competitive reactions in one system. It was reported that two different reaction times led to different products.

EXPERIMENTAL

Phenothiazine was purchased from Guangzhou Weibo Chem Ltd. All other chemicals used in the experiments were of analytical grade. Elemental analysis was performed with a Perkin Elmer 240 analyzer. IR spectra from 4000-400 cm^{-1}, as KBr pellets, were recorded on a Nicolet FT IR 170 SX pectrophotometer. Proton nuclear magnetic resonance (^1H NMR) was performed on Bruker 300 spectrometer with MS as internal startdard.

Synthesis: The synthetic route is shown in Fig. 1.

10-Ethylphenothiazine (1), 3,7-diacetyl-10-ethylphenothiazine (2) and 3,7-*bis*(2-hydrazonoethy1)-(0-ethylphenothiazine) (3) were synthesized by reported method[8].

3,7-*Bis*(2-salicylidenehydrazonoethyl-(10-ethyl-phenothiazine) (4): 3 (0.3 g) and 0.22 mL salicylaldehyde were put in methanol (25 mL) and the solution was stirred and refluxed for 30 s to yield the orange solid. Orange precipitates were

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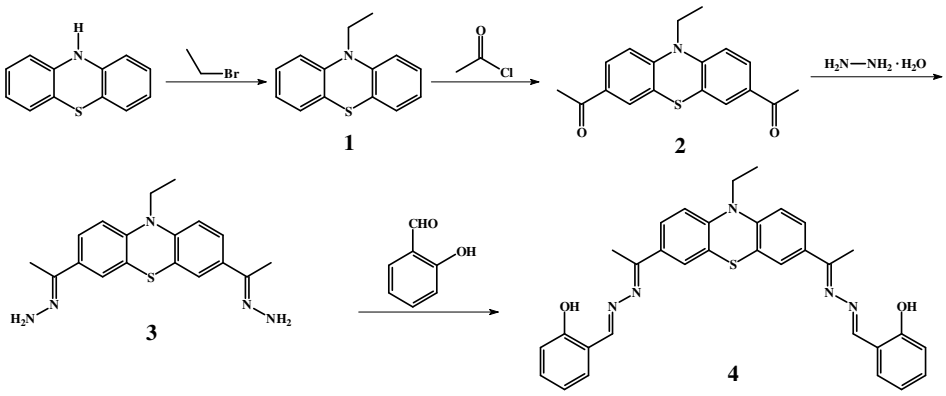


Fig. 1. Preparative steps of the compound **4**

filtered out, washed by water and ethanol and dried in vacuum. Yield: 85 %. ^{1}H NMR ($CDCl_3$ 300 MHz): 8.70(s, 2H), 7.30(s, 2H), 6.90 (d, d, d=6.90 Hz, 6H), 7.70 (t, 4H), 1.58 (s, 6H), 4.00 (m, 2H), 1.47 (t, 3H), 11.9 (d, 2H), 2.5 (s, 2H). IR (KBr, ν_{max}, cm^{-1}): 1270, 1614. MS (EI) m/z (%): 548.2 ($[M + H]^+$, 100), 413.2 (10), 391.1 (8). Ana1. calcd. (%) for $C_{32}H_{29}N_5O_2S$: C 70.18, H 5.34, N l2.79, found. (%) C 70.23, H 5.35, N l2.21.

1,2-Di(2-hydroxyl)benzylidenehydrazine (5): 3 (0.3 g) and 0.22 mL salicylaldehyde were put in methanol (25 mL) and the solution was stirred and refluxed for 40 min to yield the pale yellow crystals. Yield: 92 %. ^{1}H NMR ($CDCl_3$ 300 MHz): 8.70 (s, 2H), 7.30 (s, 2H), 7.4 (d, 2H), 7.37 (m, 2H), 6.9 (m, 2H), 7.0 (d, 2H), 2.2 (s, 2H).

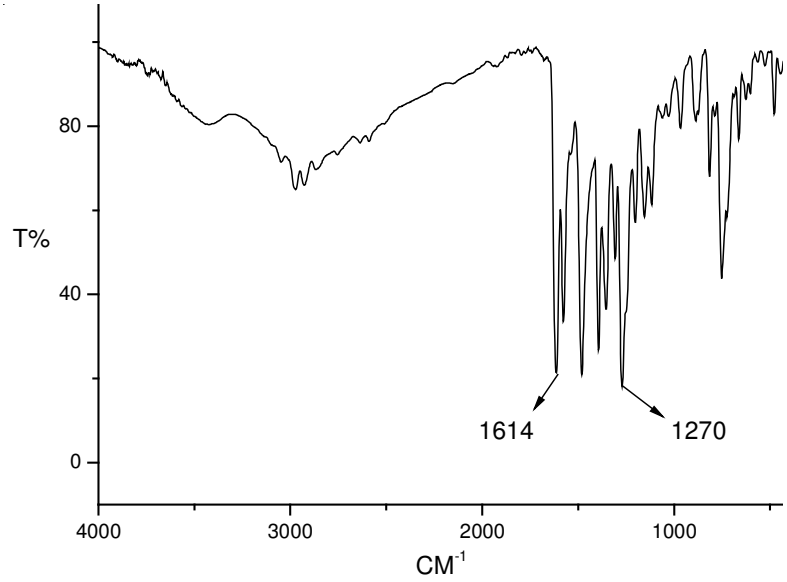
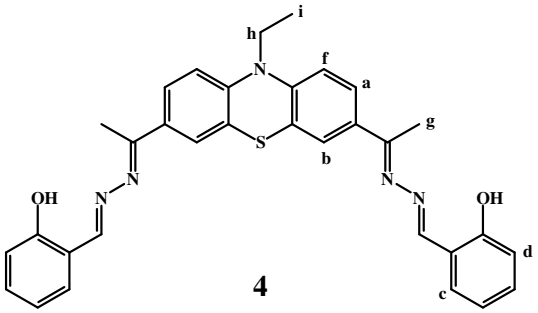


Fig. 2. Infrared of compound **4**



4

[a]H : 8.7 ppm(s) 2H, [b]H : 7.3 ppm(s) 2H, [c]H, [d]H, [f]H : 6.9 ppm (m) 6H, [e]H : 7.7 ppm(t) 4H, [g]H : 1.58 ppm(s) 6H, [h]H : 4.0 ppm (m) 2H, [i]H : 1.47 ppm(t) 3H, [j]H : 11.9 ppm(t) 2H, [k]H : 2.5 ppm(s) 2H

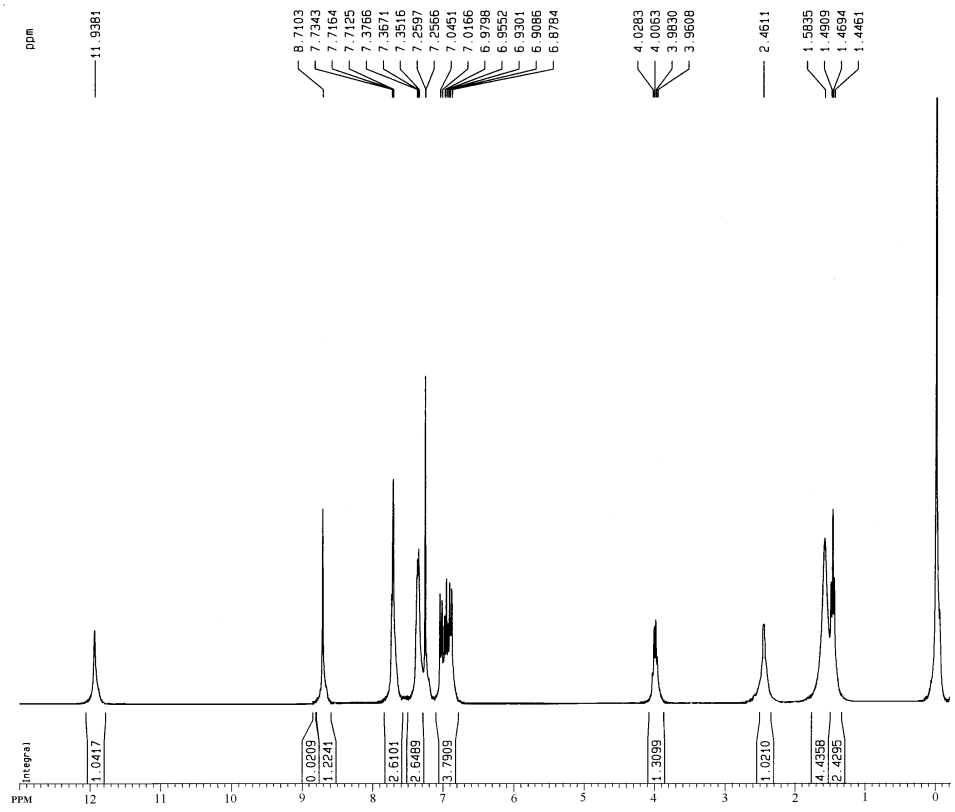


Fig. 3. [1]H NMR spectra of compound **4**

RESULTS AND DISCUSSION

4 and **5** can be obtained in the same solvent only with different reaction time. The possible reason is showed in **Scheme-II**. In the system, a slower reaction from **3-4** and a faster reaction from **3-5** are coexisting. At the same time, a reversible

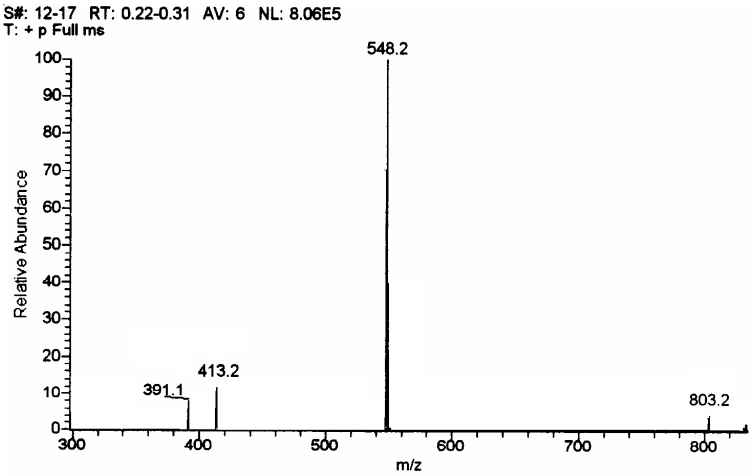
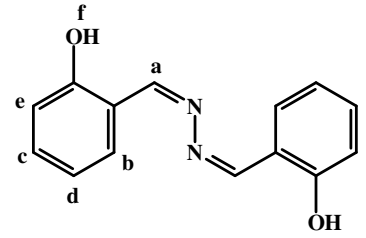


Fig. 4. MS(EI) of compound **4**



[a]H : ppm 8.7(s) 2H, [b]H : ppm 7.4(d) 2H, [c]H : ppm 7.37(m) 2H,
[d]H : ppm 6.9(m) 2H, [e]H : ppm 7.0(d) 2H, [f]H : ppm 2.2(s) 2H

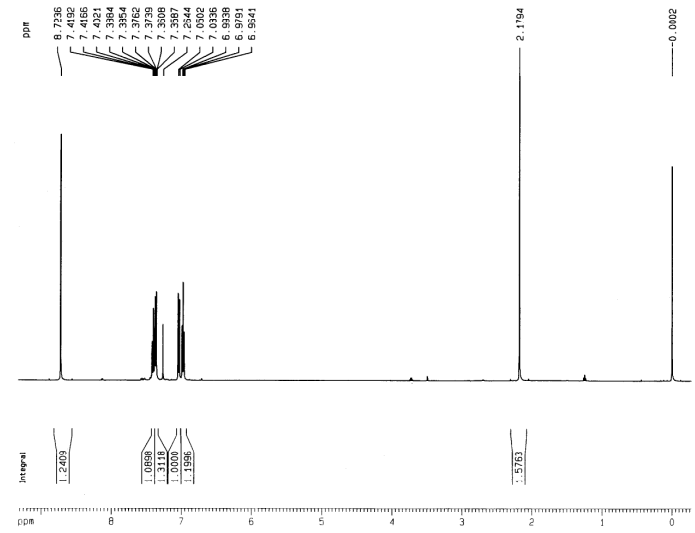
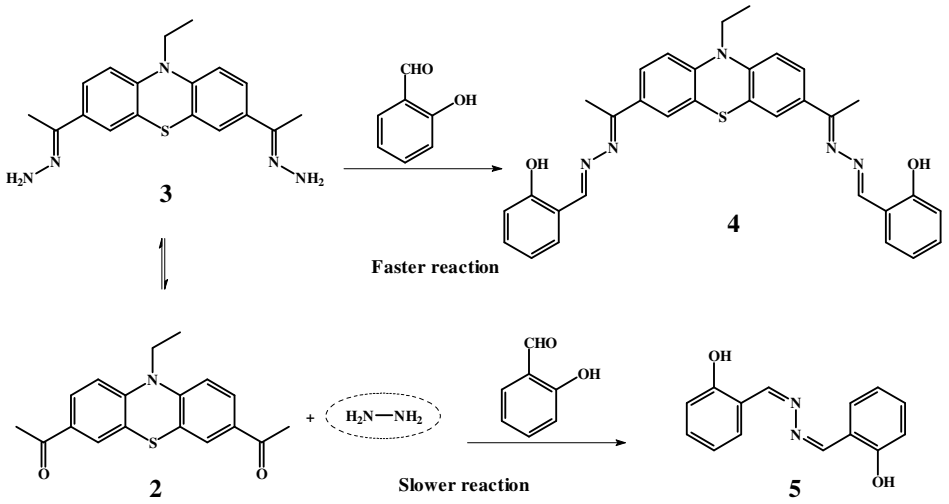


Fig. 5. [1]H NMR spectra of compound **5**

chemical reaction is between **3** and **2**. When the reactants mixed, the faster reaction works. As reaction time prolongs, the compound **5** is reformed by salicylaldehyde and hydrazine hydrate which derived from the decomposition of compound **3** because of influence of the slower reaction.



Scheme-II: Possible reason for **4** into **5**

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