SYNTHESIS OF PYRIDO[2,1-c][1,4]BENZOTHIAZINES BY REACTION BETWEEN 3-ALKOXYCARBONYLMETHYLENE4H-1,4-BENZOTHIAZINES (β ENAMINE ESTERS) AND DIMETHYL ACETYLENEDICARBOXYLATE (DMAD)

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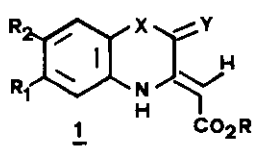
Abstract - By the title reaction pyrido[2,1-c][1,4]benzothiazines **3d,e** and **4** together with dienamine esters **2d,e,f** respectively are obtained. The latter compounds are **Z,E** Michael adducts of the enamine esters **1d-f** to DMAD, and are cyclized in high yield to the former compounds by using p-toluenesulfonic acid as catalyst. Starting from benzothiazine **1f** the phenothiazine **5** is also obtained.

Recently, Kawahara *et al.* reported[1] that pyrolysis of the quinoxalines **2a,b** yielded the corresponding pyrido[1,2-a]quinoxaline **3a,b** whereas a similar treatment of the benzoxazine **2c** did not yield the expected pyrido-compound **3c**. These results have prompted us to publish our data on the formation and intramolecular cyclization of the benzothiazines **2d-f**.

Treatment of **1f**[2] in EtOH/KOH at reflux for 3h followed by acidic workup yields the compound **1d**[3] in a shorter time and higher yield than the known method.[2]

The subsequent reaction of **1d** with equimolar amounts of DMAD in toluene at reflux for 7 h, followed by solvent evaporation and column chromatography[4] of the resulting oil afforded, in the given order, **2d**[5] and **3d**[5]. Similarly, compounds **2e**[6] and **3e**[6] were obtained starting from **1e**[2] and DMAD.



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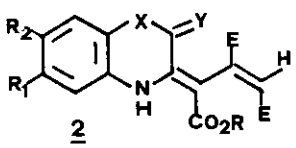

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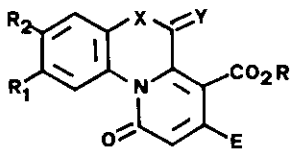


3a,b,d,e

E=CO_2Me

a) R = Me, R_1 = R_2 = H, X = NH, Y = O;

b) R = Me, R_1 = H, R_2 = Cl, X = NH, Y = O;

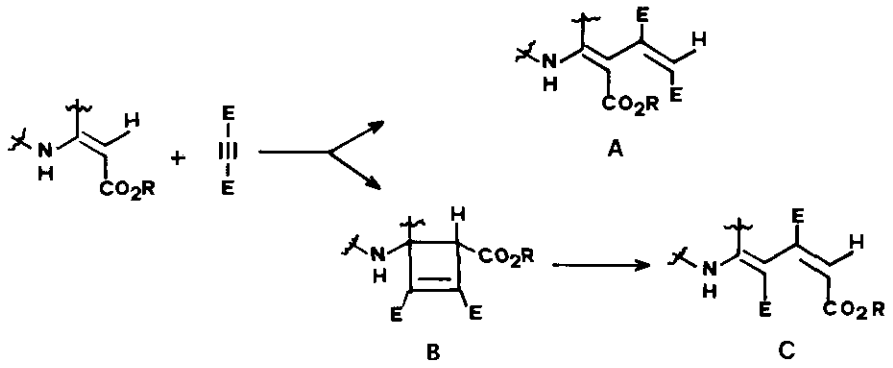
c) R = Me, R_2 = H, R_1 = Cl, X = Y = O;

d) R = Et, R_1 = R_2 = H, X = S, Y = H,H;

e) R = Me, R_1 = R_2 = H, X = S, Y = H,H;

f) R = Me, R_1 = R_2 = H, X = S, Y = H,E;

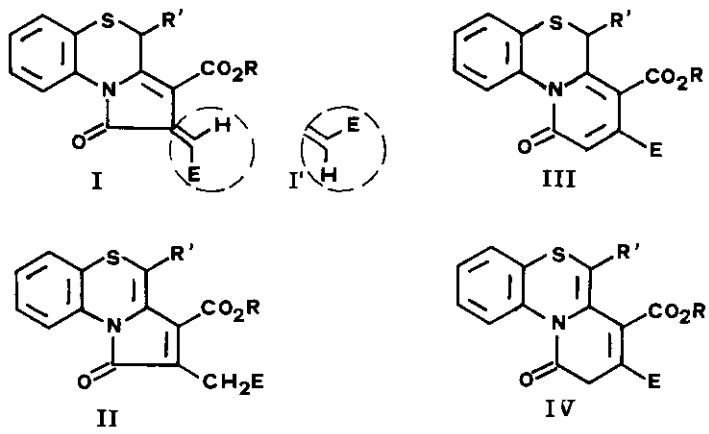
Structural elucidation of **2d** was useful to establish that the reaction between either **1d** or **1e** and DMAD yields the Michael adduct A and not the regio-isomer C which, as known, arises from ring opening of a cyclobutene adduct B.



^{1}HNMR spectrum of a **2d** sample in $CDCl_3$ shows inter alia a group of signals between δ6.8 and 7.3 originated from one vinyl proton (s at 6.93) and four aromatic protons. Overlap of absorption bands does not occur by using C_6D_6 as solvent: a well isolated one-proton singlet at δ 7.10(=CH) indicates that **2d** is one of the four expected configurational stereoisomers. The low field resonance of NH(11.56) suggests a Z-configuration at $C_\alpha = C_\beta$ double bond of the dienamine system. Futhermore, the vinyl proton of **2d** in $CDCl_3$ resonates at δ 6.93 in good agreement with 6.82 and not with 5.83 which are the reported[7] δ values for the vinyl proton of methyl Z,E-and Z,Z-5-amino-4-ethoxycarbonyl-3-methoxycarbonylsorbate respectively. Hence, Z,E configuration should be assigned to compound **2d**.

The position of the carboethoxy group in **2d** was deduced by cyclizing this compound to **3d**. In particular **2d** as well as **2e** do not cyclize in toluene at reflux unless p-toluenesulfonic acid as catalyst is added.

As regards **3d,e** structures, taking into account **2d,e** thermal stability, elemental analysis as well as spectral data suggest that such compounds arise from intramolecular cyclization of a configurational stereoisomer of **2d** or **2e** respectively by MeOH elimination. Furthermore, considering that the configurational isomer of **2d** or **2e** with E,Z geometry could undergo a 5-exo-trig ring-closure and that with E,E geometry a 5- or 6-exo-trig - ring closure, the following five structures are consistent with the spectral data.

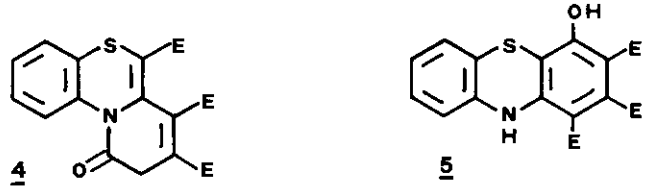


d) R=Et, R'=H; **e)** R=Me, R'=H;

The choice of the correct structure was resolved by recording the ^{1}HNMR spectrum of a **3e** protonated species and by comparing it with that of the base **3e**[6]: a significatively large downfield shift (0.45 ppm) for the singlet corresponding to the vinyl proton together with smaller shifts for all the other protons (less than 0.10 ppm) are observed. We rationalize these data considering that O-protonation of amide group[8] occurs at the structure III. Hence, the compounds **3d** and **3e** are identified as 7-alkoxycarbonyl-8-methoxycarbonyl-6H-pyrido[2,1-c][1,4]benzothiazine-10-one.

By reacting compound **1f** and DMAD in toluene at reflux for 7h three products were isolated from the reaction mixture by column chromatography[4] in the following order: dienamine **2f**[9], pyrido[2,1-c]benzo[1,4]thiazine **4**[9] and 1,2,3-trimethoxycarbonyl-4-hydroxyphenothiazine **5**[9], compound **4** being a **3f** tautomer.

Compound **2f** does not cyclize in toluene at reflux. Instead, if a trace of p-toluenesulfonic acid is added to this solution roughly quantitative cyclization to compound **4** only occurs.



4 **5**

^{1}HNMR spectra of a **2f** sample in either $CDCl_3$ or C_6D_6 are complicated by rotameric isomerism of the dienamine compound which is in Z,E geometry. This configuration is deduced from the fact that two very near singlets, due to one vinyl proton, are observed at about the same field where resonates the vinyl proton of **2d,e**.[10] The Z,E-**2f** assignement is also supported by the consideration that, under our experimental conditions, it should be difficult to isolate the other three configurational isomers of **2d**. In fact, the Z,Z-E,E[11]-and E,Z-**2f** possess the right geometry for achieving anellation to phenothiazine **5**, pyridone **4** and pyrrolinone I(R=Me,R'=E) respectively; the latter being not obtained.

The foregoing results indicate that the dienamine esters **1d-f** are useful and convenient for the synthesis of pyrido[2,1-c][1,4]benzothiazine derivatives.

REFERENCES AND NOTES

1) N.Kawahara, T.Nakajima, T.Itoh, and H.Ogura, Heterocycles, 1983,**20**,1721
N.Kawahara, T.Nakajima, T.Itoh, and H.Ogura, Heterocycles, 1984,**22**,1729.

2) P.Marchini, G.Trapani, G.Liso, and V.Berardi, Phosphorus and Sulfur, 1977, **3**,309.

3) **1d** was isolated in 47% yield by column chromatography[4] of the reaction mixture.

4) Column chromatography was performed on silica gel by using petroleum ether/ethyl acetate 8:2 as eluent.

5) **2d**(46%): yellow oil; MS m/e:377(M^+); IR(liquid film)(cm^{-1}):1725,1660,1605; ^{1}HNMR($CDCl_3$)δ:11.56(br s,1H,NH); 7.4-6.7(m,5H, aromatic+vinyl H at 6.93); 4.4-4.0(m,2H,OCH_2-);3.80(s,3H,OCH_3);3.70(s,3H,OCH_3);3.32(s,2H,SCH_2);1.20(t, 3H,CH_2-CH_3). ^{1}HNMR(C_6D_6)δ:11.82(brs,1H,NH);7.10(s,1H,vinyl H);6.4-7.0(m,4H, aromatic);4.4-3.6 (m,2H,OCH_2);3.40(s,3H,OCH_3);3.28(s,3H,OCH_3); 3.19(s,2H,SCH_2);0.97(t,3H,CH_2-CH_3).

3d(42%): red crystals, mp 178°C;MS m/e:345(M^+);IR(nujol)(cm^{-1}):1740,1720, 1670; ^{1}HNMR($CDCl_3$)δ:9.16(dd,1H,J=9 and 1Hz,aromatic); 7.47(s,1H,vinyl H); 7.3-7.0(m,3H,aromatic);4.35(q,2H,OCH_2);3.86(s,2H,SCH_2);3.69(s,3H,OCH_3); 1.34(t,3H,CH_2-CH_3).

6) **2e** (44%): yellow oil; MS m/e:363(M^+);IR (liquid film)(cm^{-1}):1725,1660,1605; ^{1}HNMR($CDCl_3$)δ:11.50(brs,1H,NH);7.4-6.7(m,5H,aromatic+vinyl H at 6.96);3.80(s,6H, OCH_3);3.70(s,3H,OCH_3);3.32(s,2H,SCH_2).

3e (43%): red crystals, mp 155°C;MS m/e:331(M^+);IR(nujol)(cm^{-1}):1740,1720,1670; ^{1}HNMR($CDCl_3$)δ:9.20(dd,1H,J=9 and 1Hz,aromatic H);7.47(s,1H,vinyl H);7.0-7.4(m,3H,- aromatic);3.86(s,5H,OCH_3+SCH_2);3.69(s,3H,OCH_3).

^{1}HNMR($CDCl_3$+CF_3COOH)δ:9.15(dd,1H,J=9 and 1Hz,aromatic H);7.92(s,1H,vinyl H);

7.1-7.5(m,3H,aromatic);4.05(s,2H,SCH_2);3.95(s,3H,OCH_3);3.74(s,3H,OCH_3).

7) N.Anghelide, C.Draghici, and D.Raileanu, Tetrahedron, 1974,**30**,623.

8) A.R.Katritzky and R.E.Reavill, J.Chem.Soc.,1963,753.

9) ***2f*** *(30%): yellow solid, mp 119°C;MS m/e:421(M^+);IR(nujol)(cm^{-1}):1760,1740,1680,* 1620;^{1}HNMR($CDCl_3$)δ:11.60 and 11.70(two brs,1H,NH);7.3-6.8(m,5H,aromatic+vinyl H as two singlets at 7.02 and 6.97);4.36 and 4.13(two s,1H,SCH);3.78,3.72,3.69 and 3.56(four s,12H,OCH_3). ^{1}HNMR(C_6D_6) δ:12.06 and 11.90(two br s,1H,NH);7.21 and 7.18(two s,1H,vinyl H);4.58 and 4.33(two s,1H,SCH);3.46,3.39,3.30,3.20 and 3.18(five s,12H,OCH_3).

4(30%): red crystals, mp 114°C;MS m/e:389(M^+);IR(nujol)(cm^{-1}):1740,1695; ^{1}HNMR($CDCl_3$)δ:8.96(dd,1H,J=9 and 1Hz,aromatic);7.3-7.0(m,3H,aromatic);3.83(s,6H, OCH_3);3.70(s,5H,OCH_3+$COCH_2$). ^{1}*HNMR(C_6D_6)δ:9.10(dd,1H,J=9 and 1Hz,aromatic);* 6.9-6.5(m,3H,aromatic);3.63(s,2H,$COCH_2$-);3.45(s,3H,OCH_3);3.32 and 3.29 (two s,6H,OCH_3).

5(21%): yellow solid, mp 159°C(from 2-propanol);MS m/e:389(M^+);IR(nujol)(cm^{-1}): 3220,1750,1700,1670;^{1}HNMR($CDCl_3$)δ:11.93(s,1H,OH exchanges with D_2O);9.87(brs,1H,NH, exchanges with D_2O);7.0-6.6(m,3H,aromatic);6.5-6.4(m,1H,aromatic);3.83,3.80 and 3.78(three s,9H,OCH_3).

10) Also the vinyl proton of the compound Z,E-**2c** in $CDCl_3$ resonates at 6.94δ *N.Kawahara, T.Nakajima, T.Itoh, H.Takayamagi, and H.Ogura,* Chem.Pharm.Bull., 1984 **32**, 1163.

11) This configurational isomer could cyclize to give the compound I'(R=Me,R'=E) also.

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