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# 4-HYDROXY-2-QUINOLONES 166*. SYNTHESIS, ISOMERISM, AND ANTITUBERCULAR ACTIVITY OF 3-ARYLAMINOMETHYLENE-QUINOLINE-2,4-(1H,3H)-DIONES

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*Condensation of 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carbaldehydes, thioglycolic acid (or methyl thioglycolate), and anilines does not lead to the synthesis of the corresponding thiazolidinylquinolones because the Schiff bases so formed exist exclusively in a form inert to enamine thioglycolates. $^1$H NMR spectroscopy showed that the main components of the isolated 3-arylaminomethylenequinoline-2,4-(1H,3H)-diones are E-isomers. The results of a study of the antitubercular properties of the compounds obtained are presented.*

**Keywords:** anilines, 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carbaldehydes, enamines, Schiff bases, isomerism, antitubercular activity, tautomerism.

The search for novel biologically active compounds with antitubercular activity has gained special urgency in the last 10-15 years. The reason for increased attention directed towards this problem has been the widespread appearance and global distribution of resistant strains of the tubercular mycobacterium which are stable to current medicinal preparations.

An interest in thiazolidin-4-ones has not diminished following the isolation in a pure state, structural identification [2], and then the synthesis [3] of actithiazic acid as an antibiotic having highly specific activity towards the mycobacterium. As a result, compounds based on this heterocycle were produced for the fight against pathogens of different mycobacterial infections [4-6] including tuberculosis [7, 8].

4-Hydroxyquinol-2-ones posses a high potential for antimycobacterial properties hence their combination with thiazolidin-4-ones in a single molecular system seems quite interesting and promising.

Thiazolidin-4-ones are obtained by a well known reaction of thioglycolic acid [9] or its esters [10] with Schiff bases. Often more simple in use is a three component condensation of an aldehyde, thioglycolic acid (alkyl thioglycolate) and primary amine [11]. The yields of the final products vary widely and this is fully

* For Communication 165 see [1].

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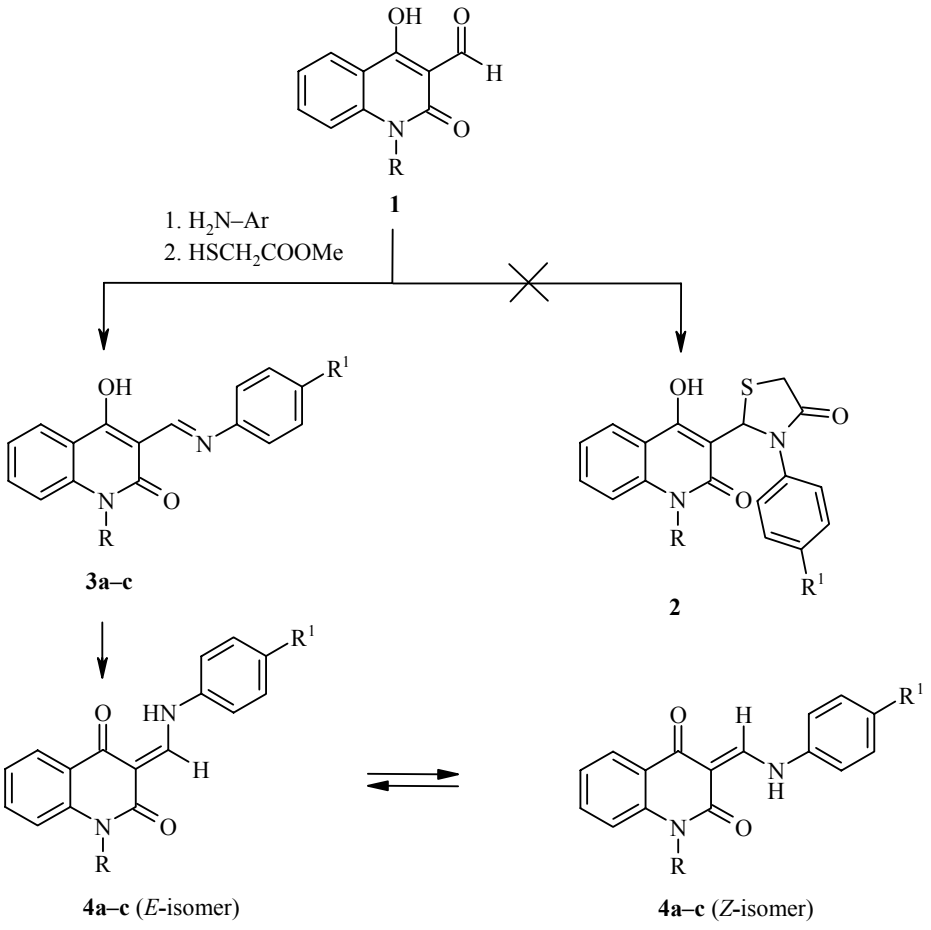
explained by structural features of the starting components. However, the corresponding thiazolidinylquinolones **2** could not be prepared at all from the 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carbaldehydes **1**.




**3**, **4 a** R = Me, $R^1$ = OEt, **b** R = $C_5H_{11}$, $R^1$ = F, **c** R = $C_5H_{11}$, $R^1$ = Cl

The reason for this is evidently the somewhat unusual structure of the light-yellow substances obtained in this way (Table 1). The $^1$H NMR spectra of these compounds (Table 2) clearly confirm the presence in their structure of just quinolone and *para*-substituted aryl fragments. In addition, doubling of some signals (in the spectra recorded with a working frequency of 400 MHz almost all of the signals are doubled) indicates that the investigated compounds in DMSO solution form a mixture of two isomers (or tautomers) in the ratio 2:1 or 3:2. The reaction products of the aldehydes **1** with anilines are undoubtedly Schiff bases. Hence it becomes clear that we are dealing with a prototropic tautomerism typical of compounds with a carbon-nitrogen double bond, i.e. azomethine–azomethine or indeed azomethine–enamine **3**↔**4** while each of these tautomers can exist further as two geometrical *Z*- and *E*-isomers [12].

To resolve this question we carried out an intensive study of one of the synthesized compounds by the $^1$H NMR method. For this *para*-ethoxy derivative there were also measured $^{13}$C NMR spectra and $^1$H–$^{13}$C heteronuclear correlation spectra through one (HMQC) and through 2-3 (HMBC) chemical bonds. It was found that doubling of the majority of the signals (see Experimental) also occurred in the carbon spectrum. Their assignment in the main component of the isomeric mixture can be made *via* the heteronuclear correlation spectra. The coordinates of the cross peaks found in the 2D HMQC and HMBC spectra are given in Table 3 for the main component of the *para*-ethoxy derivative studied.

TABLE 1. Characteristics of the 3-Arylaminomethylenequinoline-2,4-(1H,3H)-diones **4a-c**

| Compound | Empirical formula | Found, % / Calculated, % | | | mp, °C | Yield, % | Antitubercular activity. Inhibition of the growth of *M tuberculosis*, % |
|---|---|---|---|---|---|---|---|
| | | C | H | N | | | |
| **4a** | $C_{19}H_{18}N_2O_3$ | 70.67 / 70.79 | 5.54 / 5.63 | 8.77 / 8.69 | 129-131 | 91 | 29 |
| **4b** | $C_{21}H_{21}FN_2O_2$ | 71.68 / 71.57 | 6.13 / 6.01 | 8.09 / 7.95 | 122-124 | 82 | 46 |
| **4c** | $C_{21}H_{21}ClN_2O_2$ | 68.51 / 68.38 | 5.88 / 5.74 | 7.52 / 7.59 | 117-119 | 84 | 20 |

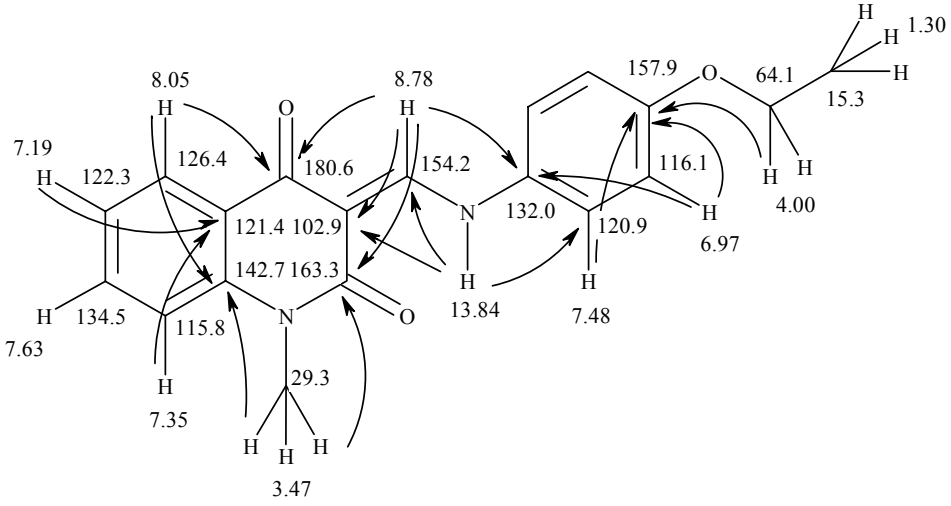
TABLE 2. $^1$H NMR Spectra of Enamines **4a-c**

| Compound | Chemical shifts, δ, ppm (200 MHz, DMSO-$d_6$), (*J*, Hz) |
|---|---|
| **4a** | 13.85 (0.63H, d, *J* = 13.6, NH *E*-isomer); 12.73 (0.32H, d, *J* = 14.0, NH *Z*-isomer); 8.81 (0.66H, d, *J* = 13.6, =CH *E*-isomer); 8.78 (0.34H, d, *J* = 14.0, =CH *Z*-isomer); 8.06 (1H, d, *J* = 8.1, H-5); 7.64 (1H, td, *J* = 8.0 and *J* = 2.3, H-7); 7.48 (2H, m, H-2',6'); 7.36 (1H, d, *J* = 8.4, H-8); 7.19 (1H, t, *J* = 7.6, H-6); 6.96 (2H, d, *J* = 8.8, H-3',5'); 4.03 (2H, q, *J* = 7.2, $OCH_2$); 3.50 (1H, s, $NCH_3$ *Z*-isomer); 3.48 (2H, s, $NCH_3$ *E*-isomer); 1.31 (3H, t, *J* = 7.2, $OCH_2C\underline{H}_3$) |
| **4b** | 13.80 (0.59H, d, *J* = 13.5, NH *E*-isomer); 12.72 (0.36H, d, *J* = 14.0, NH *Z*-isomer); 8.86 (0.61H, d, *J* = 13.5, =CH *E*-isomer); 8.81 (0.39H, d, *J* = 14.0, =CH *Z*-isomer); 8.08 (1H, dd, *J* = 8.0 and *J* = 1.5, H-5); 7.71–7.59 (3H, m, H-7,2',6'); 7.45-7.14 (4H, m, H-6,8,3',5'); 4.11 (2H, t, *J* = 7.2, $NCH_2$); 1.59 (2H, q, *J* = 6.9, $NCH_2C\underline{H}_2$); 1.33 (4H, m, $(C\underline{H}_2)_2CH_3$); 0.86 (3H, t, *J* = 6.7, $CH_3$) |
| **4c** | 13.74 (0.57H, d, *J* = 13.4, NH *E*-isomer); 12.70 (0.38H, d, *J* = 13.8, NH *Z*-isomer); 8.89 (0.6H, d, *J* = 13.4, =CH *E*-isomer); 8.83 (0.4H, d, *J* = 13.8, =CH *Z*-isomer); 8.08 (1H, dd, *J* = 8.1 and *J* = 1.5, H-5); 7.71–7.60 (3H, m, H-7,2',6'); 7.49 (2H, d, *J* = 9.0, H-3',5'); 7.38 (1H, d, *J* = 8.5, H-8); 7.20 (1H, t, *J* = 7.6, H-6); 4.11 (2H, t, *J* = 7.1, $NCH_2$); 1.58 (2H, q, *J* = 6.7, $NCH_2C\underline{H}_2$); 1.34 (4H, m, $(C\underline{H}_2)_2CH_3$); 0.86 (3H, t, *J* = 6.6, $CH_3$) |

TABLE 3. Full List of Heteronuclear $^1$H–$^{13}$C Correlations found for the Main Component of Enamine **4a**

| $^1$H signal, δ, ppm | Cross peak positions in the $^{13}$C measurements | |
|---|---|---|
| | HMQC | HMBC |
| 13.84 | — | 154.2; 132.0; 120.9; 102.9 |
| 8.78 | 154.2 | 180.6; 163.3; 132.0; 121.4; 102.9 |
| 8.05 | 126.4 | 180.6; 142.7; 134.5 |
| 7.63 | 134.5 | 142.7; 126.4; 115.8 |
| 7.48 | 120.9 | 157.9; 132.0; 116.1 |
| 7.35 | 115.8 | 121.4; 122.3 |
| 7.19 | 122.3 | 134.5; 126.4; 121.4; 115.8 |
| 6.97 | 116.1 | 157.9; 132.0 |
| 4.00 | 64.1 | 157.9; 15.3 |
| 3.47 | 29.3 | 163.3; 142.7; 115.8 |
| 1.30 | 15.3 | 64.1 |

Assignment of the signals of the protonated carbon atoms can be made from their correlation with proton signals in the HMQC spectrum and those for the quaternary carbon atoms *via* the existence of cross peaks in the HMBC spectrum. $^{1}H$ and $^{13}C$ NMR signal assignments are given in the scheme below where the arrows indicate the most significant HMBC correlations which served as the basis for carbon signal assignment. 2D COSY and NOESY spectra were used for assignment of the proton signals.




For an understanding of the isomerization in this compound the most important feature is the correlation of the NH proton signal with a chemical shift of 13.84 ppm with the carbon signal at 120.9 ppm which corresponds to the C-2' atom of the *para*-ethoxyphenyl substituent. The presence of this correlation shows that there are not more than three chemical bonds between these magnetic nuclei and this is possible only through localization of the active proton on the nitrogen atom. It was interesting that an analogous correlation was found in the minor component of the isomeric mixture. In this component the signal for the NH proton is observed at 12.72 ppm. The HMBC spectrum showed a correlation with the carbon signal at 120.8 ppm which corresponded to the C-2' atom in this isomer.

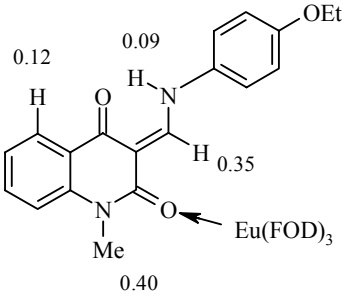
Hence the investigation carried out shows that the compound studied is the enamine **4a** which exists as a *Z*- and *E*-mixture of isomers relative to the exocyclic double bond. This conclusion was also supported by the $^{1}H$ NMR spectra measured at increased temperature. Hence heating a solution of enamine **4a** to 100ºC did not cause a signal coalescence but, in fact, just to their broadening. This suggests that there is a high energetic barrier between the isomers as is typical of *Z*- and *E*-isomers.

This is very interesting but the question as to which of these corresponds to the main isomer remains open since direct confirmatory evidence could not be obtained. An attempt to determine the $^{1}H–^{13}C$ spin-spin coupling for the carbonyl carbon atoms and the enamine =CH proton and so the answer to the question posed also was unsuccessful because the values sought were hidden by other constants. In principle, such structural problems can be resolved by comparison of intramolecular hydrogen bonds between the NH group proton and carbonyl oxygen atoms in one isomer or the other. In this way, the signal placed at lower field must undergo stronger hydrogen bonding. However, proof will not be straight forward in all cases.

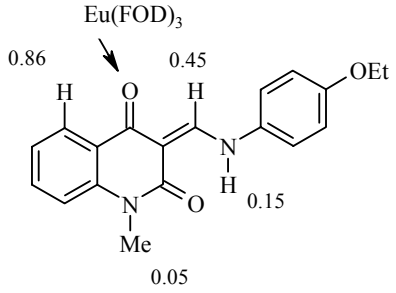
With this consideration we selected another route to resolve the problem set, bearing in mind the good solubility of enamine **4a** in chloroform and also the presence such functional groups as NH and C=O in its structure. In general these groups can coordinate efficiently with lanthanide shift reagents (LSR) leading to induced signal shifts which are useful for structural assignments in the $^{1}H$ NMR spectra. The addition of 1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane-4,6-dionate europium (III) [$Eu(FOD_3)$] to a solution of the

enamine **4a** in deuterochloroform caused a low field lanthanide induced shift (LIS) for several signals. These shifts were calculated as the difference between the chemical shifts of the corresponding sample signals with and without the LSR.

The formulae below for the main and minor isomers of enamine **4a** show these LIS values next to the corresponding protons. As is seen in the data given, the main component of the mixture shows maximal shifts for the =CH and $NCH_3$ group signals and in the minor component these are found for the =CH and aromatic quinolone H-5 proton. The closer the proton occurs to the coordination center of the molecule with the LSR the greater the LIS value proves to be. For this reason the effects seen are best explained by the stipulation that LSR coordination occurs at the carbonyl group of the heterocyclic ring which is sterically most accessible in the given isomer. Hence the observed LIS unambiguously shows that the main component of the isomeric mixture of enamine **4a** has the *E*-configuration.




*E*-**4a** (main component)




*Z*-**4a** (minor)

The structure of the Schiff base obtained by reaction of 3-acyl-4-hydroxy-2-oxo-1,2-dihydroquinolines with N-nucleophiles has repeatedly attracted the attention of investigators. As a result they have been reported as a mixture of two tautomers azomethine **3** and enamine **4** with a predominance of the latter [13-16]. The experiments we have carried out show a somewhat different picture. The 3-arylaminomethylenequinoline-2,4-(1H,3H)-diones in DMSO solution exist only as the *E*- and *Z*-forms of just the enamine tautomeric form **4**. Confirmation of this conclusion comes from both the spectroscopic investigation and also from the fact that these compounds do not take part in a reaction with methyl thioglycolate. According to a well studied mechanism for the formation of thiazolidines [17] the first stage of such reactions is the addition of thioglycolate esters at the carbon nitrogen double bond of the Schiff bases with initial formation of a C–S bond followed by closing of a thiazolidine ring. In other words, should there be an equilibrium mixture, the presence of even a small amount of azomethine **3** would certainly allow the reaction with methyl thioglycolate to occur successfully. Enamines **4** are known not to react with thioglycolates since they do not have the required C=N bond in their structure.

The antitubercular activity of the enamines **4a-c** was studied *in vitro* by a radiometric method [18, 19]. The data in Table 1 shows that at a concentration of 6.25 μg/ml the compounds studied unfortunately show little activity towards *Mycobacterium tuberculosis* H37Rv ATCC 27294. However, even in such a small series of compounds the effect of a substituent in the aniline part of the molecule of enamines **4a-c** on the biological activity is clearly seen.

## EXPERIMENTAL

$^1$H NMR spectra for the compounds synthesized were recorded on a Varian Mercury VX-200 (200 MHz) instrument.$^1$H and $^{13}$C NMR spectra for the enamine **4a**, $^1$H COSY NMR 2D spectroscopic experiments,

homonuclear Overhauser NOESY-2D, and also heteronuclear HMQC and HMBC experiments were recorded on a Varian Mercury-400 spectrometer (400 and 100 MHz for $^{1}H$ and $^{13}C$ respectively). All 2D experiments were carried out with gradient selection of useful signals. Mixing times in the pulse sequences corresponded to $^{1}J_{CH}$ = 140 and $^{2-3}J_{CH}$ = 8 Hz. The number of increments in the COSY and HMQC spectra was 128 and 400 in the HMBC spectra. The mixing time in the NOESY-2D experiment was 500 ms. The solvent was DMSO-$d_6$ or $CDCl_3$ with TMS as internal standard. The synthesis of the starting 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carbaldehydes **1** was carried out according to method reported in [1].

**3-(4-Ethoxyphenylaminomethylene)-1-methyl-quinoline-2,4-(1H,3H)-dione (4a)**. *para*-Phenetidine (*p*-ethoxyaniline) (1.37 g, 0.01 mol) and methyl thioglycolate (0.89 ml, 0.01 mol) were added to a solution of 1-methyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carbaldehyde (**1a**, 2.03 g, 0.01 mol) in dry xylene (15 ml) and refluxed for 20 h. The reaction mixture was cooled, diluted with hexane, and left for several hours in a freezer cabinet. The light-yellow precipitate of enamine **4a** was filtered off, washed with hexane, and dried. Yield 2.96 g (92%). Crystallized from a mixture of 2-propanol and hexane. $^{1}H$ NMR spectrum (400 MHz, DMSO-$d_6$), δ, ppm (*J*, Hz): 13.84 (0.65H, d, *J* = 13.6, NH *E*-isomer); 12.72 (0.29H, d, *J* = 14.0, NH *Z*-isomer); 8.78 (0.67H, d, *J* = 13.6, =CH *E*-isomer); 8.74 (0.33H, d, *J* = 14.0, =CH *Z*-isomer); 8.05 (1H, m, H-5); 7.63 (1H, m, H-7); 7.48 (2H, m, H-2',6'); 7.38 (0.33H, d, *J* = 8.4, H-8 *Z*-isomer); 7.35 (0.6H, d, *J* = 8.4, H-8 *E*-isomer); 7.19 (1H, m, H-6); 6.97 (2H, m, H-3',5'); 4.00 (2H, q, *J* = 7.2, $OCH_2$); 3.49 (1H, s, $NCH_3$ *Z*-isomer); 3.47 (2H, s, $NCH_3$, *E*-isomer); 1.30 (3H, t, *J* = 7.2, $OCH_2C\underline{H}_3$). $^{1}H$ NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 14.09 (0.68H, d, *J* = 11.6, NH *E*-isomer); 12.90 (0.22H, d, *J* = 12.4, NH *Z*-isomer); 8.96 (0.25H, d, *J* = 12.4, =CH *Z*-isomer); 8.93 (0.75H, d, *J* = 11.6, =CH *E*-isomer); 8.29 (0.25H, d, *J* = 8.0, H-5 *Z*-isomer); 8.21 (0.75H, d, *J* = 8.0, H-5 *E*-isomer); 7.59 (1H, m, H-7); 7.30-7.18 (4H, m, H-6,8,2',6'); 6.93 (2H, d, *J* = 8.8, H-3',5'); 4.03 (2H, q, *J* = 6.8, $OCH_2$); 3.59 (3H, s, $NCH_3$); 1.42 (3H, t, *J* = 6.8, $OCH_2C\underline{H}_3$). $^{1}H$ NMR spectrum (400 MHz, $CDCl_3$ + $Eu(FOD)_3$), δ, ppm (*J*, Hz): 14.18 (0.49H, d, *J* = 10.2, NH *E*-isomer); 13.05 (0.19H, d, *J* = 11.5, NH *Z*-isomer); 9.41 (0.25H, br. s, =CH, *Z*-isomer); 9.28 (0.75H, br. s, =CH *E*-isomer); 9.15 (0.25H, br. s, H-5 *Z*-isomer); 8.33 (0.75H, d, *J* = 7.2, H-5 *E*-isomer); 7.63 (1H, m, H-7); 7.40-7.24 (4H, m, H-6,8,2',6'); 6.93 (2H, d, *J* = 8.0, H-3',5'); 4.05 (2H, q, *J* = 6.4, $OCH_2$); 3.99 (2H, s, $NCH_3$ *E*-isomer); 3.64 (1H, s, $NCH_3$ *Z*-isomer); 1.43 (3H, t, *J* = 6.4, $OCH_2C\underline{H}_3$). $^{13}C$ NMR spectrum (DMSO-$d_6$), δ, ppm: 180.64 (C-4 *E*); 178.34 (C-4 *Z*); 165.32 (C-2 *Z*); 163.31 (C-2 *E*); 157.88 (C-4' *E*); 157.69 (C-4' *Z*); 154.18 (=CHNH *E*); 152.68 (=CHNH *Z*); 142.65 (C-8a *E*); 142.34 (C-8a *Z*); 134.54 (C-7); 132.22 (C-1' *Z*); 132.03 (C-1' *E*); 126.93 (C-5 *Z*); 126.44 (C-5 *E*); 122.52 (C-6 *Z*); 122.27 (C-6 *E*); 122.25 (C-4a *Z*); 121.37 (C-4a *E*); 120.88 (C-2',6' *E*); 120.80 (C-2',6' *Z*); 116.11 (C-3',5' *E*); 116.07 (C-3',5' *Z*); 115.93 (C-8 *Z*); 115.78 (C-8 *E*); 102.91 (C-3 *E*); 102.26 (C-3 *Z*); 64.08 ($OCH_2$); 29.30 ($NCH_3$ *E*); 28.61 ($NCH_3$ *Z*); 15.28 ($OCH_2\underline{C}H_3$).

**Enamines 4b,c** (Table 1) were obtained by a similar method. Previously separated enamine **4a** in the pure state, in refluxing xylene, also does not react with either thioglycolic acid or its methyl ester.

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