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# Five-Membered 2,3-Dioxo Heterocycles: XLVIII.* Reaction of 3-Aroyl- and 3-Heteroyl-2,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]-benzoxazine-1,2,4-triones with 3-Amino-5,5-dimethyl-2-cyclohexenone

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**Abstract**—3-Aroyl- and 3-heteroyl-2,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-1,2,4-triones react with 3-amino-5,5-dimethyl-2-cyclohexenone to give 3'-aroyl-4'-hydroxy-1'-*o*-hydroxyphenyl-6,6-dimethyl-2,2',3,4,5,5',6,7-octahydro-1*H*-indole-3-spiro-2'-pyrrole-2,4,5'-triones. The structure of the products was proved by X-ray analysis.

Monofunctional OH- [2] and NH-nucleophiles [3] are known to reversibly add to 3-acyl-2,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-1,2,4-triones at the carbon atom in position *3a* or *1*, while difunctional N,N- [4] and S,N-nucleophiles [5] successively attack the $C^{3a}$ atom and the $C^4$=O carbonyl group; the latter reactions are accompanied by cleavage of the benzoxazine and pyrrole rings. Reactions of 3-acyl-2,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-1,2,4-triones with C,N-dinucleophiles have not been studied.

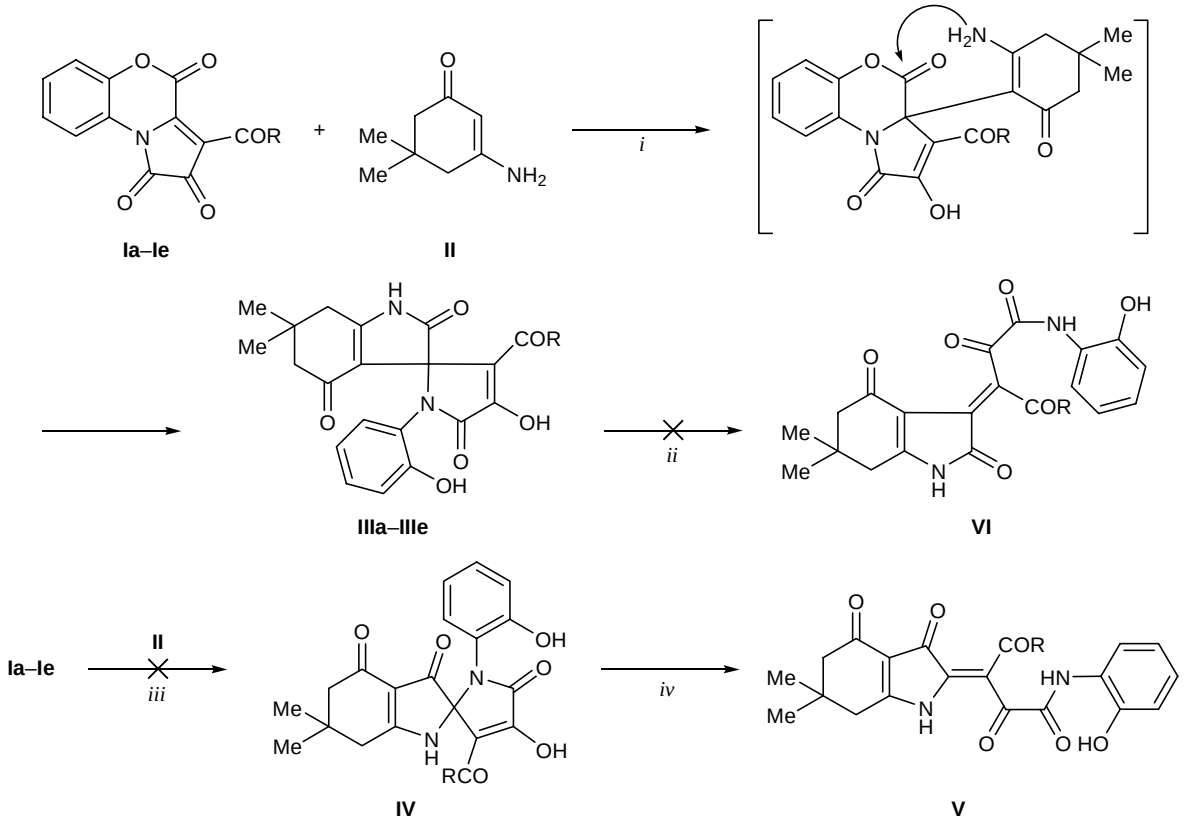
While continuing our studies of transformations of hetareno[*a*]-2,3-dihydropyrrole-2,3-diones by the action of nucleophiles, in the present work we examined reactions of 3-aroyl- and 3-heteroyl-2,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-1,2,4-triones **Ia**–**Ie** with an activated enamine, 3-amino-5,5-dimethyl-2-cyclohexenone (**II**). Compound **II** is a difunctional nucleophile possessing two approximately equivalent nucleophilic centers, β-CH and amino group. The direction of the initial attack by one of these moieties on one or another electrophilic center in molecules **Ia**–**Ie** ($C^1$, $C^2$, or $C^{3a}$) should determine the structure of the products.

The reactions of equimolar amounts of compounds **Ia**–**Ie** with enamine **II** in anhydrous acetonitrile on heating for a short time afforded individual crystalline products in high yields. However, their spectral parameters did not allow us to choose between several alternative structures **III**, **IV**, *Z*,*E*-**V**, and *Z*,*E*-**VI** (Scheme 1; only one isomer of each structure is shown). Therefore, the structure of the products was determined by X-ray analysis. According to the X-ray diffraction data, the products are 3'-aroyl-4'-hydroxy-1'-*o*-hydroxyphenyl-6,6-dimethyl-2,2',3,4,5,5',6,7-octahydro-1*H*-indole-3-spiro-2'-pyrrole-2,4,5'-triones **IIIa**–**IIIe**.

Compounds **IIIa**–**IIIe** are colorless or pale yellow crystalline substances, whih are poorly soluble in common organic solvents, readily soluble in DMF and DMSO, and insoluble in alkanes and water. They give a positive test (cherry color) for enol or phenol hydroxy group with an alcoholic solution of iron(III) chloride. The IR spectra of **IIIa**–**IIIe** contain broad absorption bands due to stretching vibrations of the phenol and enol hydroxy groups and amide N–H bond at 3360–3490 and 3160–3220 $cm^{-1}$. The lactam carbonyl bands are observed at 1740–1770 and 1710–1740 $cm^{-1}$, stretching vibrations of the enone carbonyl group ($C^4$=O) give a band at 1680–1710 $cm^{-1}$, and the aroyl (heteroyl) carbonyl group is characterized by absorption in the region 1630–1650 $cm^{-1}$.

* For communication XLVII, see [1].

**Scheme 1.**




R = phenyl (**a**), *p*-tolyl (**b**), α-naphthyl (**c**), 5-methyl-2-furyl (**d**), 2-thienyl (**e**); *i*: attack by β-CH on $C^{3a}$; *ii*: rupture of the $N^1$–$C^5$ bond; *iii*: attack by $NH_2$ on $C^{3a}$; *iv*: rupture of the $N^1$–$C^5$ bond.

In the $^1$H NMR spectra of **IIIa**–**IIIe**, we observed signals from protons in the aromatic rings and substituents attached thereto, signals from protons of the dimethylcyclohexane fragment, a singlet from the phenolic hydroxy group at δ 9.24–9.41 ppm, a singlet from the amide proton at δ 10.79–10.87 ppm, and a broadened singlet from the enol proton at δ 12.00–12.55 ppm.

Presumably, in the initial stage, the activated β-CH group of enamine **II** adds to the carbon atom in position *3*a of substrate **Ia**–**Ie**. The subsequent intramolecular cyclization via attack by the free amino group of **II** on the lactam carbonyl carbon atom in the benzoxazine ring is accompanied by cleavage of the latter at the $C^4$–$O^5$ bond. Opening of the pyrrole ring via cleavage of the $N^1$–$C^5$ bond (which was observed by us previously) [4, 5] does not occur, presumably due to greater thermodynamic stability of cyclic structures **IIIa**–**IIIe** relative to hypothetical cleavage product **VI**. In addition, 1,5-prototropic migration in **III** (which leads to structure **VI**) is likely to be more difficult than 1,3-prototropic migration in structure **IV**, leading to compound **V**. The observed transformation is a quite rare example of regioselective synthesis of difficultly accessible spiro heterocycles having various functional substituents in several positions of both heterocyclic components.

The X-ray diffraction study was performed for compounds **IIIb** and **IIId** which crystallized as the corresponding solvates. Crystals of **IIIb** were obtained as a solvate with ethyl acetate and water at a ratio of 1:1:0.5, and compound **IIId** was a 1:1 solvate with acetone. Figure 1 shows the structure of molecule **IIId**. The planar 5-methylfuroyl fragment and the pyrrole ring lie in one plane. The *o*-hydroxyphenyl fragment with the pyrrole ring forms a dihedral angle of 101°. The six-membered cyclohexenone moiety adopts an *envelope* conformation: it is folded with respect to the $C^6$–$C^8$ line through an angle of 45.1°, and the $C^7(CH_3)_2$ moiety declines toward the *o*-hydroxyphenyl substituent.

Table 1 contains the principal bond lengths in molecule **IIId**. All double bonds in the heterocyclic fragments are localized with no appreciable conjuga-

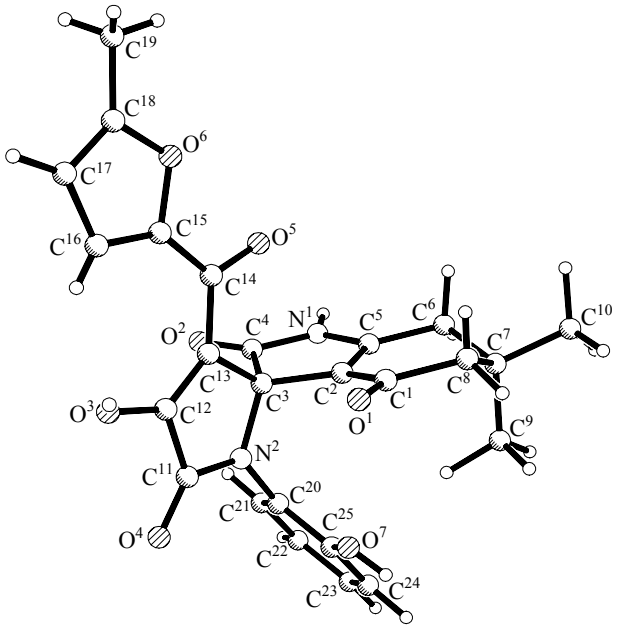


**Fig. 1.** Structure of the molecule of 4'-hydroxy-1'-*o*-hydroxyphenyl-6,6-dimethyl-3'-(5-methyl-2-furoyl)-2,2',3,4,5,5',6,7-octahydro-1*H*-indole-3-spiro-2'-pyrrole-2,4,5'-trione (**IIId**) according to the X-ray diffraction data.

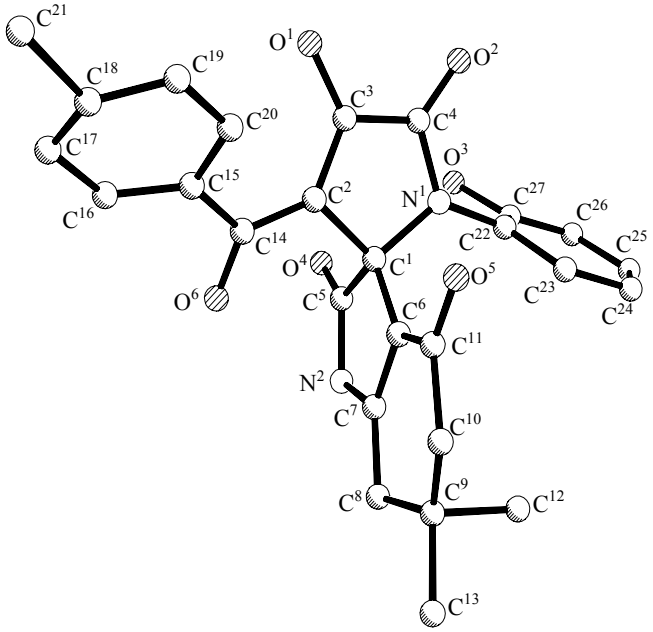


**Fig. 2.** Structure of the molecule of 4'-hydroxy-1'-*o*-hydroxyphenyl-6,6-dimethyl-3'-(*p*-toluoyl)-2,2',3,4,5,5',6,7-octahydro-1*H*-indole-3-spiro-2'-pyrrole-2,4,5'-trione (**IIIb**) according to the X-ray diffraction data.

tion. Considerable elongation of the double $C^1{=}O^1$ and $C^{14}{=}O^5$ bonds [1.248(5) and 1.244(5) Å, respectively] is explained by their participation in fairly strong intermolecular hydrogen bonds. Each molecule **IIId** in crystal is involved in two intermolecular hydrogen bonds, giving rise to infinite chains along a screw axis. In addition, acetone molecule is linked to molecule **IIId** through the hydrogen bond $O^3{-}H^3\ldots O^8$. The parameters of these bonds are listed in Table 2.

The structure of molecule **IIIb** (Fig. 2) is analogous to **IIId**. An essential difference is the configuration of the toluoyl fragment which is not planar. The torsion angle $O^6C^{14}C^{15}C^{16}$ is –25°, and the dihedral angle between the toluoyl group and the heteroring plane ($C^1C^2C^{14}O^{16}$) is –23°. However, these differences are likely to arise from specific features of crystal packing. Despite the low accuracy of the X-ray difraction data, all bond lengths and bond angles are generally consistent with available published data.

## EXPERIMENTAL

The IR spectra were obtained on a UR-20 spectrophotometer from samples dispersed in mineral oil. The $^1$H NMR spectra were recorded on a Bruker WP-400 spectrometer (400 MHz) from solutions in DMSO-$d_6$ using hexamethyldisiloxane as internal reference. The purity of the products was checked by TLC on Silufol plates using ethyl acetate–benzene (1:5) as eluent; development with iodine vapor. The analytical data are given for samples preliminarily dried at 100°C.

**Table 1.** Principal bond lengths *d* in molecule **IIId**

| Bond | *d*, Å | Bond | *d*, Å |
|---|---|---|---|
| $O^1$–$C^1$ | 1.248(5) | $O^2$–$C^4$ | 1.209(6) |
| $O^3$–$C^{12}$ | 1.344(7) | $O^4$–$C^{11}$ | 1.225(5) |
| $O^5$–$C^{14}$ | 1.244(5) | $O^6$–$C^{18}$ | 1.352(6) |
| $O^6$–$C^{15}$ | 1.381(5) | $O^7$–$C^{20}$ | 1.381(6) |
| $N^1$–$C^4$ | 1.376(6) | $N^1$–$C^5$ | 1.383(6) |
| $N^2$–$C^{11}$ | 1.363(6) | $N^2$–$C^{25}$ | 1.421(6) |
| $N^2$–$C^3$ | 1.482(6) | $C^1$–$C^2$ | 1.407(6) |
| $C^1$–$C^8$ | 1.502(7) | $C^2$–$C^5$ | 1.348(6) |
| $C^2$–$C^3$ | 1.503(6) | $C^3$–$C^{13}$ | 1.498(6) |
| $C^3$–$C^4$ | 1.553(7) | $C^5$–$C^6$ | 1.493(7) |
| $C^6$–$C^7$ | 1.542(7) | $C^7$–$C^8$ | 1.518(7) |
| $C^7$–$C^{10}$ | 1.535(8) | $C^7$–$C^9$ | 1.532(8) |
| $C^{11}$–$C^{12}$ | 1.466(7) | $C^{12}$–$C^{13}$ | 1.339(6) |
| $C^{13}$–$C^{14}$ | 1.458(7) | $C^{14}$–$C^{15}$ | 1.424(7) |
| $C^{15}$–$C^{16}$ | 1.351(7) | $C^{16}$–$C^{17}$ | 1.393(9) |
| $C^{17}$–$C^{18}$ | 1.332(8) | | |

**Table 2.** Parameters of hydrogen bonds in molecule **IIId**

| D–H···A | D–H (Å) | H···A (Å) | D···A (Å) | ∠DHA (deg) |
|---|---|---|---|---|
| $N^1$–$H^1$···$O^1$ [a] | 0.80 | 2.05 | 2.75 | 146.5 |
| $O^7$–$H^7$···$O^5$ [b] | 0.83 | 1.93 | 2.68 | 149.7 |
| $O^3$–$H^3$···$O^8$ | 0.85 | 1.75 | 2.64 | 179.9 |

[a] 1/2 – *x*, 1/2 + *y*, 1/2 – *z*.
[b] 1/2 – *x*, –1/2 + *y*, 1/2 – *z*.

**Table 3.** Principal crystallographic parameters of compounds **IIId** and **IIIb** and conditions of X-ray diffraction experiment

| Parameter | **IIId** | **IIIb** |
|---|---|---|
| Formula | $C_{25}H_{22}N_2O_8 \cdot C_3H_6O$ | $C_{27}H_{24}N_2O_6 \cdot C_2H_5OH \cdot 0.5H_2O$ |
| *a*, Å | 9.577(2) | 19.369(4) |
| *b*, Å | 12.603(3) | 13.978(3) |
| *c*, Å | 21.876(4) | 20.829(4) |
| α, deg | 90.00 | 90.00 |
| β, deg | 96.80(3) | 90.00 |
| γ, deg | 90.00 | 90.00 |
| *V*, Å$^3$ | 2621.8(1) | 5639(2) |
| *Z* | 4 | 8 |
| Space group | *P*2(1)/*n* | *Pbcn* |
| *M* | 520.52 | 527.56 |
| *d*, g/cm$^3$ | 1.319 | 1.243 |
| *F*(000) | 1096 | 2232 |
| μ, mm$^{-1}$ | 0.097 | 0.090 |
| Diffractometer | KM-4 (KUMA Diffraction) | |
| Radiation | Mo$K_\alpha$ | |
| $\theta_{max}$, deg | 25.08 | 23.08 |
| Number of reflections | 4176 | 3959 |
| Number of reflections with $I > 2s(I)$ | 1253 | 758 |
| Number of refined parameters | 419 | 155 |
| *R*-Factor [$I > 2s(I)$] | 0.0472 | 0.1276 |
| *R*-Factor (all reflections) | 0.2728 | 0.4472 |
| *GOOF* | 0.817 | 0.999 |

The principal crystallographic parameters of compounds **IIIb** and **IIId** and conditions of the X-ray diffraction experiment are summarized in Table 3. The calculations were performed with the aid of SHELX86 and SHELX97 software packages [6, 7]. The structure of molecule **IIId** was refined in the full-matrix anisotropic approximation. The positions of methyl hydrogen atoms were determined from the geometry considerations, and the other hydrogen atoms were localized objectively by the difference synthesis of electron density. The structure of **IIIb** was not refined in anisotropic approximation, and hydrogen atoms were not localized, because of insufficient number of experimental reflections (the crystals were of a poor quality). The coordinates of atoms are available from the authors.

**4'-Hydroxy-1'-*o*-hydroxyphenyl-6,6-dimethyl-3'-benzoyl-2,2',3,4,5,5',6,7-octahydro-1*H*-indole-3-spiro-2'-pyrrole-2,4,5'-trione (IIIa).** A solution of 1.0 mmol of compound **Ia** and 1.0 mmol of enamine **II** in 10 ml of anhydrous acetonitrile was heated for 5 min under reflux. The mixture was cooled, and the precipitate was filtered off. Yield 0.38 g (83%), mp 203–205°C (from acetone). IR spectrum, ν, cm$^{-1}$: 3470, 3220 br (OH, NH); 1770, 1720 ($C^5$=O, $C^2$=O), 1710 ($C^4$=O); 1640 (PhCO). $^1$H NMR spectrum, δ, ppm: 0.74 s (3H, Me), 0.87 s (3H, Me), 2.00 s (2H, $C^7H_2$), 2.21 d.d and 2.35 d.d (2H, $C^5H_2$, *J* = 18.1 Hz), 6.74–7.69 m (9H, $H_{arom}$), 9.41 s (1H, OH, phenol), 10.87 s (1H, NH), 12.20 br.s (1H, OH enol). Found, %: C 68.09; H 4.88; N 6.03. $C_{26}H_{22}N_2O_6$. Calculated, %: C 68.11; H 4.84; N 6.11.

Compounds **IIIb**–**IIIe** were synthesized in a similar way.

**4'-Hydroxy-1'-*o*-hydroxyphenyl-6,6-dimethyl-3'-(*p*-toluoyl)-2,2',3,4,5,5',6,7-octahydro-1*H*-indole-3-spiro-2'-pyrrole-2,4,5'-trione (IIIb).** Yield 87%, mp 228–230°C (from acetonitrile). IR spectrum, ν, cm$^{-1}$: 3400, 3180 br (OH, NH); 1750, 1710 ($C^5$=O, $C^2$=O); 1700 ($C^4$=O); 1650 ($C_6H_4CO$). $^1$H NMR spectrum, δ, ppm: 0.73 s (3H, Me), 0.85 s (3H, Me), 1.97 s (2H, $C^7H_2$), 2.21 d.d and 2.34 d.d (2H, $C^5H_2$, *J* = 18.1 Hz), 6.72–7.60 m (8H, $H_{arom}$), 9.24 s (1H, OH, phenol), 10.79 s (1H, NH), 12.00 br.s (1H, OH, enol). Found, %: C 68.66; H 5.11; N 5.87. $C_{27}H_{24}N_2O_6$. Calculated, %: C 68.63; H 5.12; N 5.93.

**4'-Hydroxy-1'-*o*-hydroxyphenyl-6,6-dimethyl-3'-(1-naphthoyl)-2,2',3,4,5,5',6,7-octahydro-1*H*-indole-3-spiro-2'-pyrrole-2,4,5'-trione (IIIc).** Yield 89%, mp 214–215°C (from acetonitrile). IR spectrum,

ν, $cm^{-1}$: 3430, 3120 br (OH, NH); 1740, 1710 ($C^5$=O, $C^2$=O); 1690 ($C^4$=O); 1630 ($C_{10}H_7CO$). $^1$H NMR spectrum, δ, ppm: 0.75 s (3H, Me), 0.88 s (3H, Me), 2.00 s (2H, $C^7H_2$), 2.22 d.d and 2.34 d.d (2H, $C^5H_2$, *J* = 18.1 Hz), 6.74–8.30 m (11H, $H_{arom}$), 9.29 s (1H, OH, phenol), 10.85 s (1H, NH), 12.05 br.s (1H, OH, enol). Found, %: C 70.78; H 4.82; N 5.45. $C_{30}H_{24}N_2O_6$. Calculated, %: C 70.86; H 4.76; N 5.51.

**4'-Hydroxy-1'-*o*-hydroxyphenyl-6,6-dimethyl-3'-(3-methyl-2-furoyl)-2,2',3,4,5,5',6,7-octahydro-1*H*-indole-3-spiro-2'-pyrrole-2,4,5'-trione (IIId).** Yield 88%, mp 197–199°C (from acetone). IR spectrum, ν, $cm^{-1}$: 3360, 3160 br (OH, NH); 1770, 1740 ($C^5$=O, $C^2$=O); 1680 ($C^4$=O); 1640 (C=O, furoyl). $^1$H NMR spectrum, δ, ppm: 0.70 s (3H, Me), 0.92 s (3H, Me), 1.94 d.d and 2.01 d.d (2H, $C^7H_2$, *J* = 16.2 Hz), 2.17 d.d and 2.35 d.d (2H, $C^5H_2$, *J* = 18.0 Hz), 2.35 s (3H, Me in furyl), 6.38–7.57 m (6H, $H_{arom}$), 9.34 s (1H, OH, phenol), 10.84 s (1H, NH), 12.51 br.s (1H, OH, enol). Found, %: C 64.97; H 4.78; N 5.97. $C_{25}H_{22}N_2O_7$. Calculated, %: C 64.93; H 4.80; N 6.06.

**4'-Hydroxy-1'-*o*-hydroxyphenyl-6,6-dimethyl-3'-(2-thenoyl)-2,2',3,4,5,5',6,7-octahydro-1*H*-indole-3-spiro-2'-pyrrole-2,4,5'-trione (IIIe).** Yield 86%, mp 222–224°C (from acetone). IR spectrum, ν, $cm^{-1}$: 3490, 3220 br (OH, NH); 1760, 1720 ($C^5$=O, $C^2$=O); 1680 ($C^4$=O); 1630 (C=O, thenoyl). $^1$H NMR spectrum, δ, ppm: 0.71 s (3H, Me), 0.90 s (3H, Me), 1.95 d.d and 2.02 d.d (2H, $C^7H_2$, *J* = 16.1 Hz), 2.18 d.d and 2.36 d.d (2H, $C^5H_2$, *J* = 17.9 Hz), 6.74–8.10 m (7H, $H_{arom}$), 9.38 s (1H, OH, phenol), 10.84 s (1H, NH), 12.55 br.s (1H, OH, enol). Found, %: C 62.03; H 4.36; N 5.94. $C_{24}H_{20}N_2O_6S$. Calculated, %: C 62.06; H 4.34; N 6.03.

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