Coumarin-enaminoester Adducts: Structure Corrections (X-ray) and Some Novel Transformations. Synthesis of Annulated Tricyclic 2-Pyridones

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Abstract: By means of X-ray crystallographic analysis the correct structure of all three types of stable coumarin-enaminoester adducts **6**, **10** and **11** and the corresponding spontaneous multistep heterocyclizations of ANRORC-type are reported. The initially formed adducts **3**–**5** undergo lactone ring opening as well as, in many cases, spontaneous transannular intramolecular Michael addition, to give **6**, **10** and **11**. A classic Michael addition of ethyl malonamate **12** to 3-substituted coumarins **1** followed by a lactone ring opening gives **13** as final product.

Key words: enamines, N-heterocycles, pyridines, pyrans, Michael addition, X-ray analysis

In a series of previously published papers[1a–d] the Michael addition of enaminoesters **2a**–**c** to coumarin (**1a**), 6-nitrocoumarin (**1f**) and their derivatives (**1b**–**e**,**g**–**i**) with electron-withdrawing 3-substituents (EWG) was described. On the basis of their spectral properties (IR, ^{1}H NMR, ^{13}C NMR, MS) the structures of types **3**,**4** and **5** (Scheme 1), or their tautomeric forms, were assumed at that time. Some of these structures, unfortunately incorrect, also appeared in Houben-Weyl.[2]

Since there has been hesitation concerning the interpretation of some ^{1}H NMR resonance signals (for example NH or OH) the assigned structures **3**–**5** have always remained doubtful. The following facts played the most important role for those assignments: There was no absorption band for any free phenolic OH group in the IR spectra of any of the adducts which were chloroform-soluble. Instead, there was a peak in the MS (EI) spectra with *m/z* equal to the molecular mass of the corresponding starting enamine **2**. It was possible to interpret this defragmentation as a reverse elimination of the 4-substituent from **3**–**5** to give the corresponding starting coumarins **1a**–**i** whose molecular masses were often detectable in the mass spectra (EI). Hence, we believed that the coumarin skeleton remained unchanged in the adducts. In some degradation trials we were even able to isolate the starting coumarin, for instance after heating the adduct with trifluoroacetic acid.

Meanwhile, we succeeded in growing crystals of some of the coumarin-enaminoester adducts so that they became suitable for X-ray crystallographic analysis. We wish to report now the true structure of the coumarin-enaminoester adducts according to the X-ray data of some stable end products[3] of each type (Figure 1, Figure 2, Figure 3) as well as some of their simple chemical transformations. All of these new results show that we made the wrong assumption many years ago.

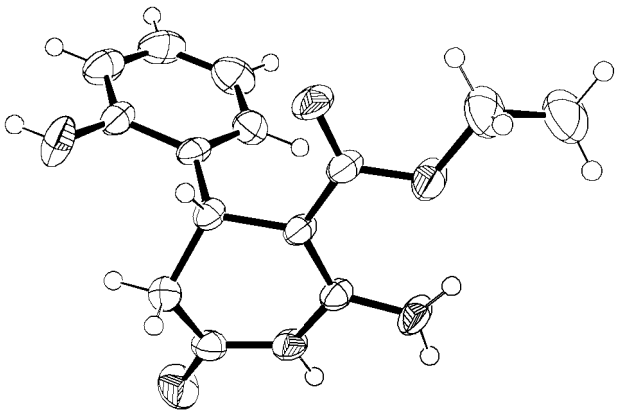

Figure 1 X-ray structure of **6a** at the 50% probability level

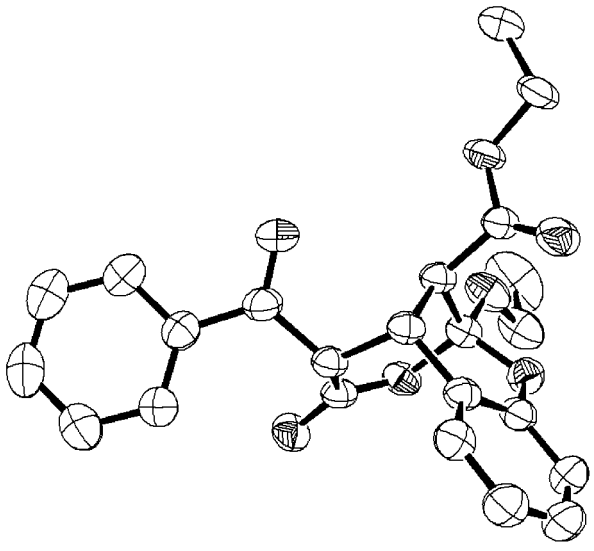

Figure 2 X-ray structure of **10e**[4] at the 50% probability level (H-atoms are omitted for greater clarity)

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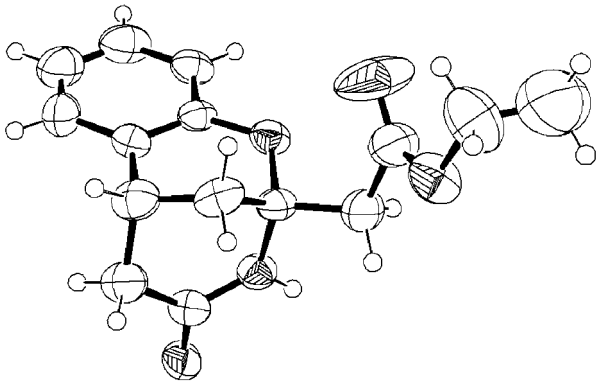
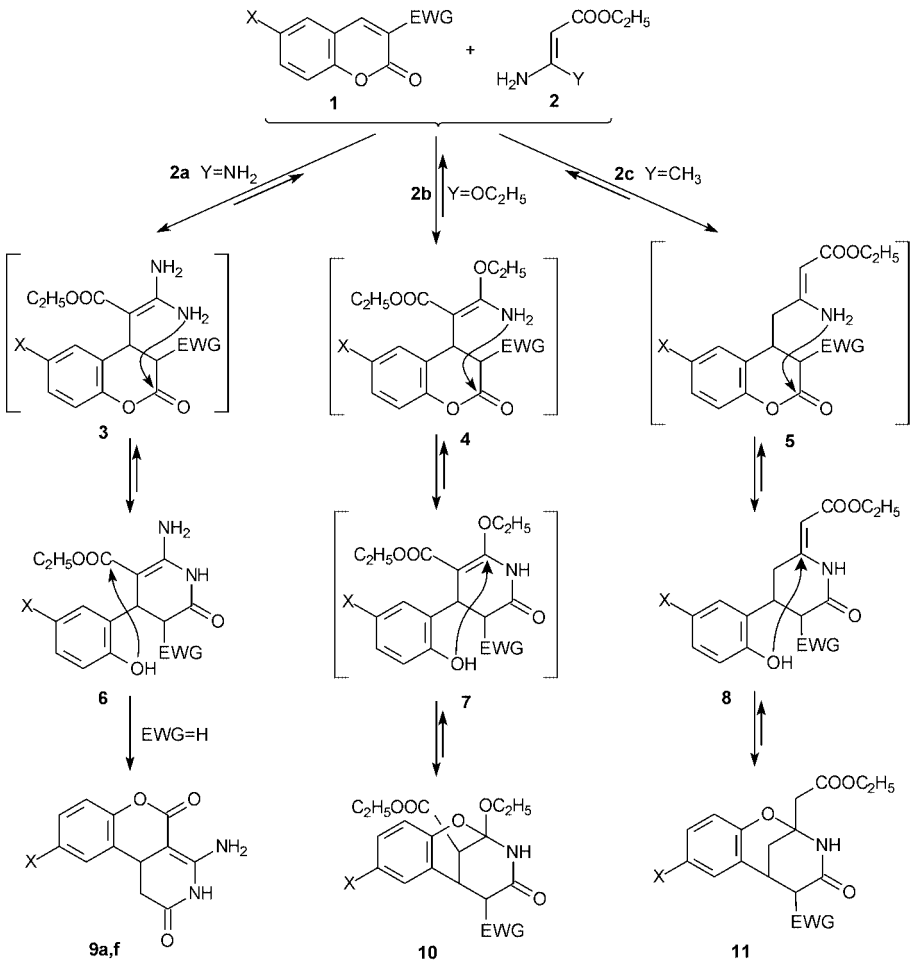


Figure 3 X-ray structure of **11a**[4] at the 50% probability level

Addition of three types of 3-aminopropenoates **2a**–**c** was carried out in our studies (Scheme 1; Table 1). While the 3,3-diamino (**2a**) and the 3-amino-3-ethoxy (**2b**) propenoates react with their α-carbon to give initially the intermediate adducts **3** and **4**, respectively, the aminocrotonate **2c** adds predominantly with its γ-carbon atom.[1a–c] It turned out that the initially formed 1:1 C-adducts of types **3**–**5** are thermodynamically unstable and undergo intramolecular rearrangements spontaneously through an ANRORC mechanism to form the 2-pyridones **6**–**8**, of which **6** and **8** are isolatable. Surprisingly, the intermediates **7** and **8** cyclize via further intramolecular Michael addition of the phenolic hydroxyl group to the conjugated double bond and, as an end result, the corresponding stable tricycles **10** and **11** are built. The 4-(*o*-hydroxyphenyl)-2-pyridones **6a**,**f** can be purposely cyclized on heating, or catalytically, to give benzopyrano[3,4-*c*]pyridines **9a**,**f** whose correct structures have already been reported.[1b,c]

Compounds with structures similar to **10** or **11**, containing a carbon, oxygen or sulfur 1,3-transannular bridge, were



1, 3-11	a	b	c	d	e	f	g	h	i
X	H	H	H	H	H	NO_2	NO_2	NO_2	NO_2
EWG	H	COOH	$COOC_2H_5$	$COCH_3$	COC_6H_5	H	COOH	$COOC_2H_5$	$COCH_3$

Scheme 1 Three types of non-isolatable, initially formed, coumarin-enaminoester adducts **3**, **4** and **5**. They undergo further intramolecular rearrangements to the stable end products **6**, **10** and **11**. Compounds **9a**,**f** are obtainable from **6a**,**f** on heating.[1a,c]

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Table 1 Reactants, Corrected Structures (**6**, **8**, **10**, **11**), Former Structures (**3**, **4**, **5**, **8**) and Some Experimental Data for the Coumarin-enaminoester Adducts

Reactants (conditions)[4]	Product, correct structure	Product, former structure[a]	Yield,[1a–c] (%)	Mp,[1a–c] (°C)
1a + **2a** (EtOH, r.t., 5 days)	**6a** (X-ray, Figure 1)	**3a** (**4a**[1a,2]; **3**[1b]; **4**[1d])	65	190–193
1b + **2a** (EtOH, reflux, 5 h)	**6a** (X-ray, Figure 1)	**3a** (**4a**[1a,2]; **3**[1b]; **4**[1d])	44	192–195
1c + **2a** (EtOH, r.t., 24 h)	**6c**	**3c** (**4c**[1a,2])	47	122–125
1e + **2a** (EtOAc, r.t., 5 h)	**6e**	**3e** (**4d**[1a,2])	49	153–156
1f + **2a** (EtOH, r.t., 4 d)	**6f**	**3f** (**5a**[1c])	84	Dec.>200
1g + **2a** (EtOH, reflux, 10 h)	**6f**	**3f** (**5a**[1c])	53	Dec.>200
1h + **2a** (EtOH, r.t., 7 d)	**6h**	**3h** (**5c**[1c])	58	Dec.>170
1i + **2a** (EtOH, r.t., 14 d)	**6i**	**3i** (**5d**[1c])	59	155–158
1b + **2c** (EtOH, reflux, 30 h)[b]	**8a** (X-ray)[3]	**8a** (**12**[1b])	40	153–155
1c + **2b** (EtOH, r.t., 48 h)	**10c**	**4c** (**3c**[1a])	67	112–115
1d + **2b** (EtOH, reflux, 20 h)	**10d**	**4d** (**3e**[1a])	49	146–148
1e + **2b** (EtOH, reflux, 20 h)	**10e**[4] (X-ray, Figure 2)	**4e** (**3d**[1a])	49	153–155
1f + **2b** (EtOH, reflux, 35 h)	**10f**	**4f** (**3c**[1c])	8	169–172
1g + **2b** (EtOH, reflux, 8 h)	**10f**	**4f** (**3c**[1c])	56	167–171
1h + **2b** (EtOH, r.t., 5 d)	**10h**	**4h** (**3e**[1c])	74	130–133
1i + **2b** (EtOH, r.t., 2 d)	**10i**	**4i** (**3d**[1c])	84	139–140
1b + **2c** (EtOH, reflux, 30 h)[b]	**11a**[4] (X-ray, Figure 3)	**5a** (**11**[1b])	25	153–156
1c + **2c** (EtOH, reflux, 52 h)	**11c**	**5c** (**8** [1a])	50	143–145
1i + **2c** (EtOH, reflux, 32 h)	**11i**	**5i** (**6b**[1c])	8	132–135

[a] Formula numbers as assigned in the corresponding original paper[1a–d] are given in parentheses.
[b] A mixture of products **8a** and **11a** was obtained from **1b** + **2c**; separated by column chromatography on silica gel.[1b]

reported earlier by Claremon et al.[5] However, their synthesis has been accomplished in a completely different way. The authors did not mention whether or not the transannular nucleophilic addition of the phenolic OH group occurred spontaneously, as it takes place in **7** or **8** (Scheme 1).

Most spectral data for the stable products **6a**,**c**,**e**,**f**,**h**,**i**, **8a**, **10c**–**f**,**h**,**i** and **11a**,**c**,**i** were already published in our previous communications,[1a–c] which also describe their detailed preparation procedures.[4] Some experimental data together with the references for these compounds are summarized here in Table 1. The structures of the remaining adducts, which could not be analyzed by means of X-ray measurements, have been deduced solely from the compatibility of their spectral characteristics, above all, from their NMR spectra. That is, all compounds of the **6**-series (Table 1) show analogous ^{1}H NMR spectra (outside the region of the aromatic protons). The same applies to the **10**-series and to the **11**-series. For instance, the ^{1}H- and ^{13}C NMR spectra of the products **6a** and **6f**, which differ only by the 6-nitro group, are consistent with each other.[6,7]

The adducts **6h** and **10c** could be converted by acidic hydrolysis into glutarimide derivatives **13h** and **13c**, respectively (Scheme 2), whose constitution was confirmed by means of X-ray analyses. Similarly, acidic hydrolysis of **6f** and **10h**,**i** lead to the glutarimides **13f**,**h**,**i**, which were independently synthesized by simple Michael addition of ethyl malonamate **12** to the coumarins **1c**,**g**,**h**,**i** in the presence of triethylamine.[1a,c] The initially formed Michael adducts **14** (not isolatable) surprisingly undergo spontaneous intramolecular cyclization to yield the stable end products **13** (the intermediate **14g** after decarboxylation). In our previous papers,[1a,c] the assumed structure **14** was incorrect because we never realized that the amide NH_2 group, being a very weak nucleophile, would attack and open the lactone ring. Obviously, the (*o*-hydroxyphenyl)-glutarimide derivatives of type **13** possess greater stability than **14**.

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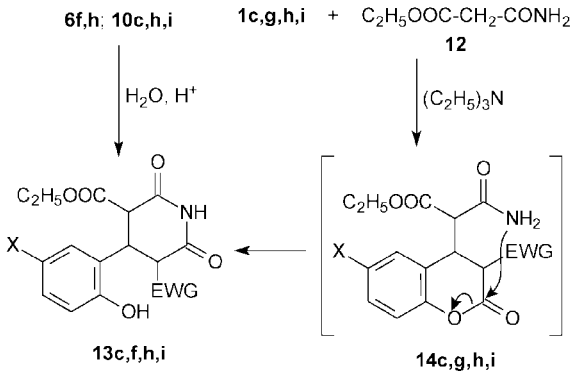
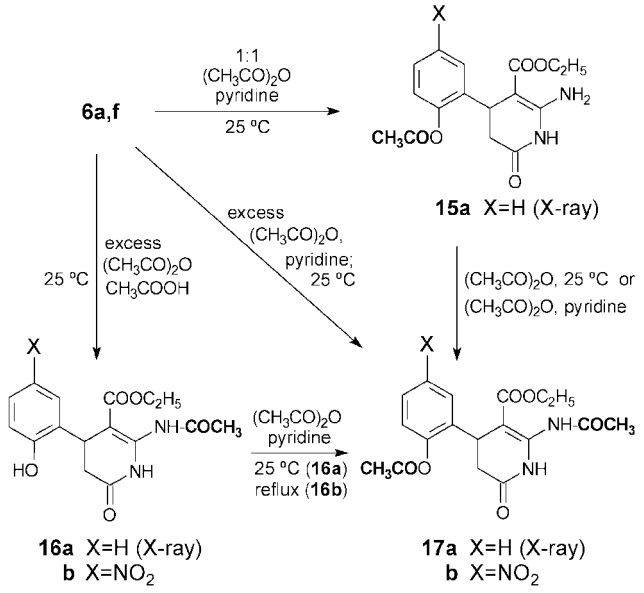


13, 14	EWG	X
c	$COOC_2H_5$	H (X-ray)
f	H	NO_2
g	COOH	NO_2
h	$COOC_2H_5$	NO_2 (X-ray)
i	$COCH_3$	NO_2

Scheme 2 Preparation of glutarimide derivatives **13**.



Scheme 3 Acetylation of **6a**,**f**

Compounds **6a**,**f** have been additionally characterized by acetylation (Scheme 3). Appropriate reaction conditions have been worked out for each of the possible acetyl derivatives **15**–**17**. Thus, **15a** and **16a**,**b** were obtained by treatment of **6a**,**f** with acetic anhydride at room temperature in the presence of pyridine or acetic acid, respectively. The O,N-diacetyl derivative **17a** was prepared by treatment of **6a** with excess of acetic anhydride in pyridine, or by acetylation of each of the monoacetyl derivatives (Scheme 3). Our attempts to achieve selective O-acetylation of **6f** in order to prepare **15b** (X = NO_2, Scheme 3) failed and, therefore, compound **17b** could be obtained solely by refluxing **16b** with acetic anhydride in pyridine. Apparently, the nitro group deactivates O-acetylation under milder conditions. The constitution of three compounds **15a**, **16a** and **17a**, was established by X-ray analysis,[3] which allowed to unambiguously determine the chemical shifts of the corresponding signals in the ^{1}H NMR spectra of all five acetyl derivatives.[6,7] In our previous papers[1b,d] the structure of the O-acetyl derivative **15a** was erroneously ascribed to the N-acetyl compound **16a**.

In conclusion, we would like to emphasize that all multistep intramolecular transformations of the initial adducts **3**–**5** into **6**,**8**,**10**,**11** occur spontaneously, apparently under thermodynamic control. In order to explain the presence in the MS (EI) spectra of peaks with *m/z* equal to the molecular mass of the starting coumarin **1a**–**i**, full reversibility of these processes (Scheme 1) must be assumed. This reversibility has also been confirmed by the conversion of **6a**,**10c** into the starting coumarins **1a**,**c** by refluxing with diluted *p*-toluenesulfonic or trifluoroacetic acid in anhydrous acetonitrile.[8]

Nonetheless, the Michael addition of enamino esters to electrophilic coumarins (**1a**–**i**) seems to be a useful route to the tricyclic structures of the types **9**–**11**.

Acknowledgment

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References

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(3) **X-ray Crystal Structure Analyses**: atomic coordinates, bond lengths [Å] and angles [deg], anisotropic displacement parameters, hydrogen coordinates, torsion angles [deg] have been deposited at Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, under deposition numbers CCDC 177460 for **6a**, CCDC 177461 for **8a**, CCDC 177459 for **10e**, CCDC 181931 for **11a**, CCDC 233450 for **13c**, CCDC 177462 for **13h**, CCDC 177463 for **15a**, CCDC 177464 for **16a**, CCDC 177464 for **17a** [fax: +44 (1223)336033; homepage: http://www.ccdc.cam.ac.uk].

(4) (a) **Typical Procedure for the Preparation of Coumarin-enaminoester Adducts (6a,c,e,f,h,i; 8a; 10c–f,h,i; 11a,c,i):** A mixture of 15 mmol of the corresponding coumarin **1a**–**i** and 15 mmol of an enaminoester **2a**–**c** in 40 mL anhyd EtOH was stirred (temperature and period of time are given in Table 1). After cooling, the separated crystals of the corresponding adduct were filtered, washed with cold EtOH and recrystallized, usually from EtOH. If a mixture of products was obtained (TLC monitoring), the solvent was removed in vacuo and the residue was separated by column chromatography on siliga gel.
(b) Systematic names: Ethyl 12-benzoyl-9-ethoxy-11-oxo-8-oxa-10-azatricyclo[7.3.1.$0^{2,7}$]trideca-2 (7),3,5-triene-13-carboxylate (**10e**); Ethyl {11-oxo-8-oxa-10-azatricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6-trien-9-yl}acetate (**11a**).

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(6) **Ethyl 2-Amino-4-(2-hydroxyphenyl)-6-oxo-1,4,5,6-tetrahydro-3-pyridinecarboxylate (6a) (unpublished data)**: ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.02 (t, J = 7.0 Hz, 3 H, CH_3), 2.51 (d, ^2J = 16.0 Hz, 1 H, 5-H_A), 2.80 (dd, ^2J = 16.0 Hz, ^3J = 7.3 Hz, 1 H, 5-H_B), 3.99 (m, 2 H, OCH_2), 4.35 (d, ^3J = 7.3 Hz, 1 H, 4-H), 6.67 (m, 1 H, 6′-H), 6.80 (m, 2 H, 3′-H, 5′-H), 6.99 (m, 1 H, 4′-H), 6.00–8.00 (br, 2 H, NH_2), 9.45 (s, 1 H, NH or OH), 9.59 (s, 1 H, OH or NH). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 13.5 (CH_3), 28.7 (C-4), 36.1 (C-5), 57.4 (O-*C*H$_2$), 74.9 (C-3), 114.0 ($C_{arom.}$), 117.9 ($C_{arom.}$), 125.5 ($C_{arom.}$), 126.5 ($C_{arom.}$), 128.4 ($C_{arom.}$), 152.4 (C-2′), 153.4 (C-2), 167.4 (C=O, ester), 170.0 (C=O, lactam).
Salient NMR signals: O-Acetyl derivative (**15a**): mp 170–172 °C (toluene). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.32 (s, 3 H, $OCOCH_3$), 7.03–7.25 (m, 6 H, 4H_{arom} and NH_2), 9.73 (s, 1 H, lactam-NH). N-Acetyl derivative (**16a**): mp 184–186 °C (EtOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.21 (s, 3 H, $NCOCH_3$), 9.61 (br s, 1 H, OH), 10.68 (s, 1 H, amide-NH), 11.49 (s, 1 H, lactam-NH). O,N-Diacetyl derivative (**17a**): mp 180–181 °C (EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.23 (s, 3 H, $NCOCH_3$), 2.34 (s, 3 H, $OCOCH_3$), 10.96 (s, 1 H, amide-NH), 11.98 (s, 1 H, lactam-NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0 (OCO*C*H$_3$), 25.3 (NCO*C*H$_3$).

(7) **Ethyl 2-Amino-4-(2-hydroxy-5-nitrophenyl)-6-oxo-1,4,5,6-tetrahydro-3-pyridinecarboxylate (6f) (unpublished data)**: ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.04 (m, 3 H, CH_3), 2.50 (d, ^2J = 16.2 Hz, 1 H, 5-H_A), 2.80 (dd, ^3J = 7.3 Hz, ^2J = 16.2 Hz, 1 H, 5-H_B), 3.95 (m, 2 H, OCH_2), 4.40 (d, ^3J = 7.3 Hz, 1 H, 4-H), 7.01 (d, 1 H, 3′-H), 7.75 (s, 1 H, 6′-H), 8.03 (d, 1 H, 4′-H), 6.20–7.80 (br, 2 H, NH_2), 9.80 (s, 1 H, NH or OH), 11.35 (br s, 1 H, OH or NH). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 14.8 (CH_3), 30.5 (C-4), 36.9 (C-5), 58.6 (O-CH_2), 75.0 (C-3), 115.9 ($C_{arom.}$-3′), 123.1 ($C_{arom.}$-6′), 124.7 ($C_{arom.}$-4′), 131.7 ($C_{arom.}$-1′), 139.8 ($C_{arom.}$-5′), 154.6 (C-2), 162.0 ($C_{arom.}$-2′), 168.2 (C=O, ester), 170.3 (C=O, lactam).
Salient ^{1}H NMR signals: N-Acetyl derivative (**16b**): mp 218–220 °C (2-PrOH). ^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.23 (s, 3 H, $NCOCH_3$), 10.72 (s, 1 H, amide-NH), 11.40 (s, 1 H, lactam-NH), 11.5 (br s, 1 H, OH). O,N-Diacetyl derivative (**17b**): mp 165–166.5 °C (2-PrOH). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.29 (s, 3 H, $NCOCH_3$), 2.40 (s, 3 H, $OCOCH_3$), 11.12 (s, 1 H, amide-NH), 12.01 (s, 1 H, lactam-NH).

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