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Synthetic approaches of *N*-α-hydroxyalkyl amides or urea derivatives are described. In particularly, a new 1,4,6-oxadiazocine-2,5,8-trione was obtained by condensation of glyoxylic acid on urea derivatives in acidic catalysis condition.

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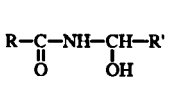

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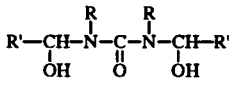

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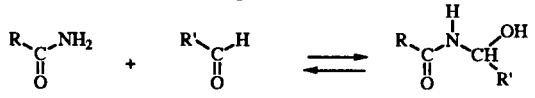
N-α-Hydroxyalkylamides or urea derivatives **1** and **2** represent important key intermediates for the synthesis of numerous pharmacologically active drugs [1]. We have investigated the reactivity of glyoxylic acid derivatives on various ureas. It is known that only reactive aldehydes like formaldehyde, chloral and glyoxylic acid and its esters react on amides leading to fairly stable *N*-α-hydroxyalkyl amides [2,3] (equation 1).

Equation 1



only when R' = H, CCl_3, CO_2R''

This reaction is an equilibrium process which usually disfavors the adduct in the case of non activated aldehydes. In the literature, there are no examples of condensation of glyoxylic acid derivatives on urea. In order to achieve the synthesis of *N*-α-hydroxy-β-functionalized urea intermediates, we have investigated the reactivity of various disubstituted ureas (Scheme 1) firstly with glyoxylic acid derivatives, secondly with chloroglyoxylate derivatives and thirdly with dimethyl tartrate.

Condensation of Glyoxylic Acid Derivatives on *N,N'*-substituted Urea.

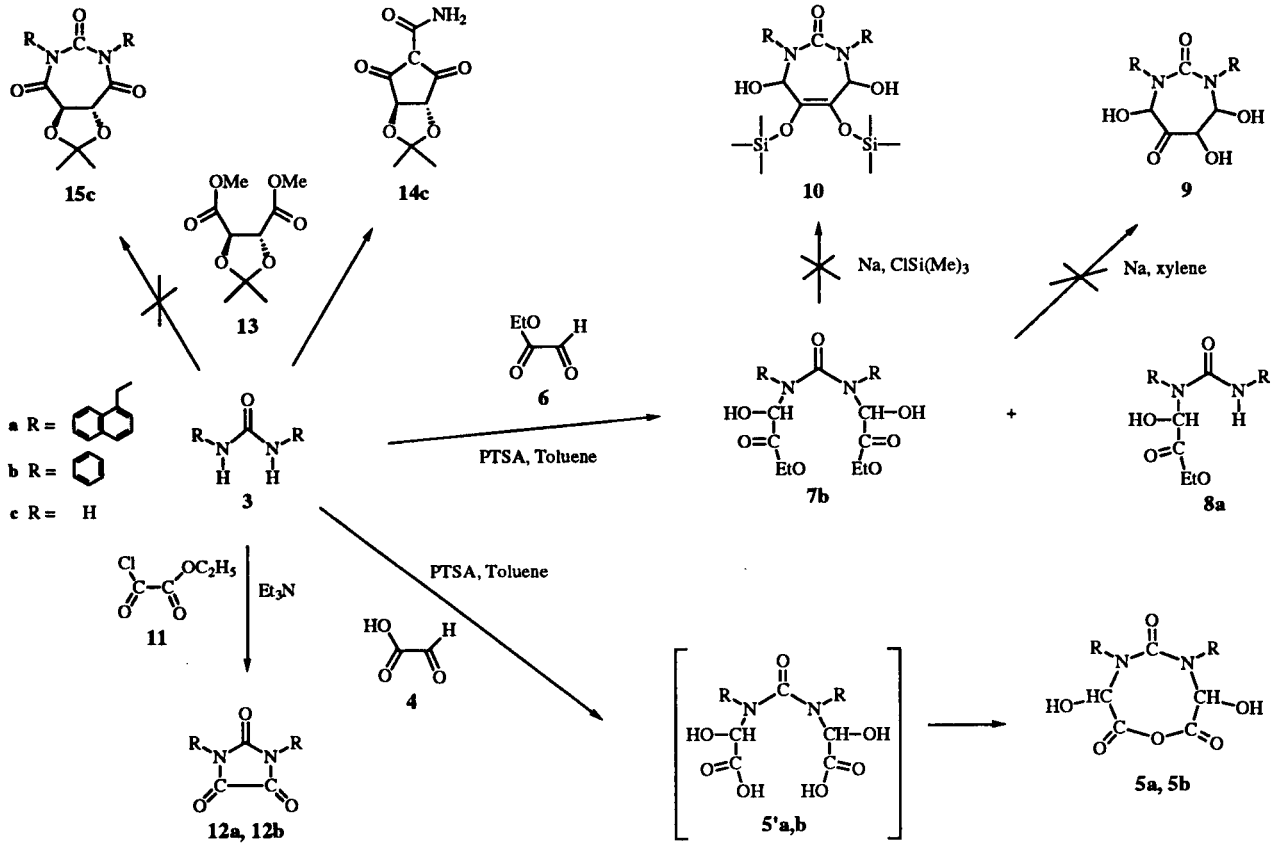
The ease of formation of *N*-dihydroxy-β-functionalized ureas depends, among other factors, on the nature of glyoxylic moiety. Unexpectedly, when glyoxylic acid itself **4** was condensed in hot toluene on substituted urea **3a**, **3b** in acidic catalysis conditions (*para*-toluenesulfonic acid) led to new 1,4,6-oxadiazocine-2,5,8-triones **5a** and **5b**. Surprisingly the formation of the expected α-dihydroxyalkyl-β-dicarboxylic acid was not observed. If the temperature of condensation was lowered, no reaction occured, but in any case the corresponding dicarboxylic intermediate **5'** was not observed. To our knowledge, it is the first time that such 1,4,6-oxadiazocine-2,5,8-triones are reported. Their chemical structures were established on the basis of spectrometric data (^{13}C, ^1H nmr, ms, ir) (Table 1) and elemental analyses.

Interconversion of carboxylic acids to acid anhydrides is a well-known reaction and has been well-documented in literature [4]. Usually this reaction proceeds through the formation of the corresponding acid chloride intermediate or through an activation of the carboxylic acid function by the use of various carbodiimide catalysts [4]. Symmetrical anhydrides have been also obtained through the use of dehydratation reagents (supported phosphorus pentoxide in toluene at 100°) [5]. Considering the experimental conditions (*para*-toluenesulfonic acid, toluene,

Table 1
Physical and Spectroscopic Data of 1,4,6-Oxadiazocane-2,5,8-trione

No.	R	Yield	Formula	Rf	IR C=O	^1H NMR	MS [M+1]$^+$
5a		16%	$C_{27}H_{22}N_2O_6$	0.4 Toluene/ Ethyl acetate 97/3	1601 urea 1713 anhydride	1.65 (s, 2H, OH), 4.20 and 5.75 (dd, 2H, CH_2 *syn*, J = 14 Hz), 5.25 (dd, 2H, CH_2 *anti*, J = 14 Hz), 7.10 (dd, 2H, CH, J = 7 Hz), 7.30-8.40 (m, 14 H, H arom)	471
5b		78%	$C_{17}H_{14}N_2O_6$	0.7 Toluene/ Ethyl acetate 75/25	1610 urea 1725 anhydride	1.62 (s, 2H, OH), 2.37 (s, 2H, CH-OH), 7.20-7.60 (m, 10 H, H arom)	343

Scheme 1



100°) used to obtain the 1,4,6-oxadiazocane-2,5,8-trione derivatives, it is obvious that the reaction proceeds *via* an α-thermical dehydratation process.

It should be emphsized that the oxadiazocinetrione resulting from the condensation of glyoxylic acid **4** on diphenylurea **3b** (carbanilide) led to the highest yield (45%) while the dinaphthylmethylurea **3a** gave a lower yield (16%).

In contrast, when glyoxylic acid ester **6** was condensed with the above mentioned ureas, the expected di and mono-*N*-α-hydroxy-β-carboxylic esters **7b** and **8a** were obtained in reasonable yields (70% and 40% repectively) (Scheme 1).

Acyloin condensation with these urea adducts was attempted under different experimental conditions reported in the literature, sodium in refluxing benzene or xylene [6], or in liquid ammonia [7] in order to obtain the corresponding seven-membered cyclic acyloin **9**. This cyclisation failed regardless of the experimental conditions; only polymeric by-products were isolated. Some examples of seven-membered cyclic acyloins were reported [8], as well as other unsuccessful attempts [9] but in any case, the synthesis of seven-membered cyclic substituted urea acyloin have been reported. Similar acyloin condensation on the urea diester **7b** was attempted using an excess of sodium in the presence of chlorotrimethylsilane in order to generate the corresponding dialkylsilyl ethers **10**. Under these conditions the desired intermediate **10** was not formed.

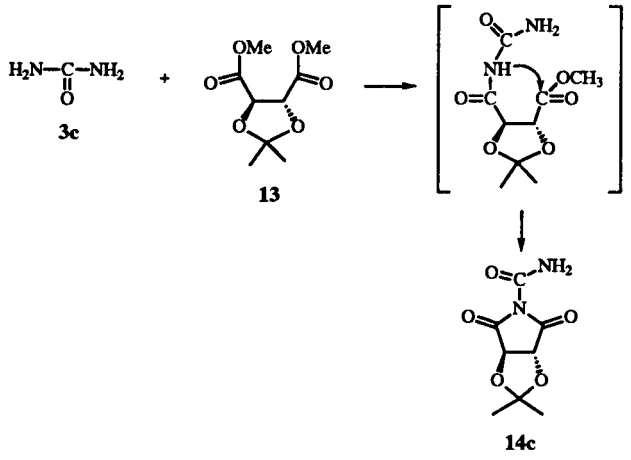
Condensation of Chloroglyoxylate Derivatives on *N,N'*-substituted Ureas.

When ethyl chloroglyoxylate **11** was condensed with *N,N'*-substituted ureas, only the formation of the *N,N'*-substituted imidazoline-2,4,5-trione derivatives **12a** and **12b** was observed (Scheme 1). In this case the formation of the five membered ring heterocycle was favoured, *versus* the formation of the possible diadduct as mentioned in the case of the condensation of glyoxylic acid ester **7b**.

Condensation of Dimethyl 2,3-*O*-Isopropylidene-L-tartrate with *N,N'*-substituted Ureas.

Expecting the formation of seven-membered ring cyclic urea (**15**) we have investigated the condensation of protected tartrate **13** with various ureas [10]. The reaction was conducted by refluxing a solution of urea in ethanol in the presence of sodium ethoxide **11**. Only urea **3c** itself reacted with tartrate under the experimental conditions. *N,N'*-Substituted ureas **3a** and **3b** failed to react under these conditions. The same results were observed when other conditions (potassium *tert*-butoxide in refluxing

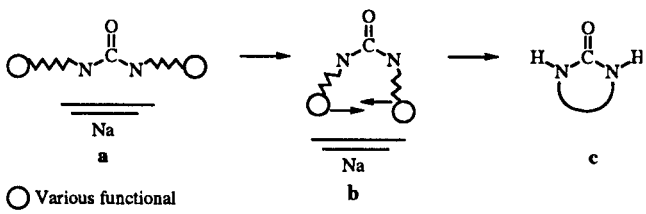
Scheme 2



toluene, sodium hydride in hot *N,N*-dimethylformamide, potassium hydroxide in refluxing ethanol) were investigated. Moreover, only the formation of the five membered cyclic compound **14c** was observed. These results can be explained since, generally speaking, urea itself is more reactive than a substituted urea, and also because after the first addition of tartrate with urea, cyclisation occured through the condensation on the maleimido nitrogen atom rather than with the primary urea nitrogen atom. Therefore, the formation of the thermodynamically most stable five membered cylic adduct **14c** is favored (Scheme 2).

From the results obtained, it appears that cyclisation reactions involving urea derivatives are thermodynamically controled processes, which depend mainly on geometrical and structural features of the condensing reagents (glyoxylic acid, glyoxylic acid ester, ethyl chloroglyoxylate, tartrate). Acyloin condensation involving a disubstituted β-carboxylic acid ester substituted urea failed, probably because when we examined the rational for acyloin cyclisation, three steps could be considered (Figure 1):

Figure 1



○ Various functional groups

a) The electrophilic carbon atoms of the ω-diester are attracted to the sodium surface.

b) The translational energy motion available sliding on the metal surface.

c) Ring closure.

Due to the presence of the urea function, the translational energy required in step 2 represents an energetic barrier hindering the seven-membered ring acyloin formation. In contrast, the formation of unexpected eight-membered 1,4,6-oxadiazocine trione ring during the condensation of glyoxylic acid with the disubstituted urea indicates that the loss of a molecule of water leading to the eight-membered ring is a thermodynamically possible process.

As expected, condensation of chloroglyoxylate with disubstituted ureas on the one hand, and dimethyl tartrate with ureas on the other hand, led to the expected thermodynamically favored five-membered heterocyclic ring to provide **12a**, **12b**, **14c**.

EXPERIMENTAL

Nuclear magnetic resonance spectra were recorded with a Bruker AMX-200 or AMX-400 (^{1}H nmr; ^{13}C nmr). Chemical shift values are expressed in δ values (part per million) relative to residual chloroform 7.24 ppm. FAB$^+$ mass spectra were obtained on a JEOL DX-100 mass spectrometer (Laboratoire de Mesures Physiques-RMN, USTL, Montpellier, France) using a cesium ion source. Infrared spectra were obtained using a Perkin-Elmer 1605 FT-IR spectrophotometer, values are expressed in cm^{-1}. Melting points were determined using MEL-TEMP II, Laboratory Devices, in sealed tubes and are uncorrected. Preparative flash column chromatography was performed using silica gel Merck G60 230-240 mesh. Analytical thin-layer chromatography was performed on silica gel plates, 60 F_{254} aluminium (Merck, DarMStadt) 0.2 mm thickness. Glyoxylic acid monohydrate, ethyl oxalyl chloride, urea, diphenylurea, phosgene in toluene, (-)-dimethyl-2,3-*O*-isopropylidene-L-tartrate and all reaction solvents were used from sealed bottles and were purchased from Aldrich Company. Ethyl glyoxylate was prepared by using a known procedure [11].

1,3-Bis(1-naphthylmethyl)urea (**3b**).

To a cooled (0°) solution of 3 g (23.6 mmoles) of 1-naphthalenemethylamine and 3.25 g (32.5 mmoles) of triethylamine in toluene (120 ml) was added dropwise a solution of 1.59 g (11.2 mmoles) of phosgene in toluene. The mixture was allowed to warm up to room temperature and stirred for 2 hours. The reaction mixture was poured into 0.5 *N* solution of hydrochloric acid (50 ml) and stirred for 1 hour. The resulting solution was filtered under reduced pressure. The resulting precipitate was collected and dried to give **3b**, 2.43 g (67%) as a white solid, mp 250°; Rf = 0.34 (toluene/ethyl acetate: 4/1); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 4.74 (d, 4H, CH_2, J = 5.6 Hz), 6.47 (t, 2H, NH, J = 5.6 Hz), 7.46-8.17 (m, 14 H, H arom), ^{13}C nmr (dimethyl sulfoxide-d_6): δ 45.1 (CH_2), 123.5-136.0 (C_{arom}), 157.0 (C=O).

Anal. Calcd. for $C_{23}H_{20}N_2O$: C, 81.14; H, 5.92; N, 8.22; O, 4.69. Found: C, 80.91; H, 5.89; N, 8.20; O, 4.67.

4,6-Bis(1-naphthylmethyl)-3,7-dihydroxyperhydro-1,4,6-oxadiazocine-2,5,8-trione (**5a**).

Glyoxylic acid **4** (17 mg, 0.17 mmole) was refluxed in toluene for 1 hour using a Dean-Stark apparatus. Then 30 mg (0.08 mmole) of **3a** was added with a catalytic amount of *p*-toluenesulfonic acid and the resulting mixture was stirred at reflux for 5 hours. The mixture was then cooled to room temper-

ature, water was added and the organic layers were extracted with toluene (3 x 5 ml), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by preparative layer chromatography 1 mm (eluent: toluene) to obtain **5a**, 6 mg (16%); Rf = 0.38 (toluene/ethyl acetate: 97/3); ^{1}H nmr (deuteriochloroform): δ 1.65 (s, 2H, OH), 4.20 and 5.75 (dd, 2H, CH_2 *syn*, J = 14 Hz), 5.25 (dd, 2H, CH_2 *anti*, J = 14 Hz), 7.10 (dd, 2H, CH, J = 7 Hz), 7.30-8.40 (m, 14 H, H arom); ms: [M+H] = 471; ir (potassium bromide): ν CO urea 1601, CO anhydride 1713.

Anal. Calcd. for $C_{27}H_{22}N_2O_6$: C, 68.92; H, 4.71; N, 5.95; O, 20.40. Found: C, 69.10; H, 4.70; N, 5.96; O, 20.42.

4,6-Diphenyl-3,7-dihydroxyperhydro-1,4,6-oxadiazocine-2,5,8-trione (**5b**).

Using a Dean-Stark apparatus, to a refluxing solution of 520 mg (2.45 mmoles) of diphenylurea **3b** in toluene (30 ml) was added 497 mg (5.40 mmoles) of glyoxylic acid **4** and 47 mg (0.25 mmole) of *p*-toluenesulfonic acid. The resulting mixture was heated under reflux for 48 hours. The mixture was cooled to room temperature and toluene was removed under reduced pressure. Water was then added and the aqueous layer was extracted with ethyl acetate (3 x 15 ml). The combined organic layers were washed with 5% solution of sodium bicarbonate (15 ml), water (15 ml) and dried over anhydrous sodium sulfate. After concentration the residue was purified by flash-chromatography over silica gel (toluene) to give **5b**, 693 mg (78%); Rf = 0.67 (toluene/ethyl acetate: 75/25); ^{1}H δ 1.62 (s, 2H, OH), 2.37 (s, 2H, CH-OH), 7.20-7.60 (m, 10 H, H arom); ^{13}C nmr (deuteriochloroform): δ 64.3 (CH-OH), 127.1-136.8 (C arom), 154.0 (C=O urea), 169.5 (C=O anhydride); ms: [M+H] = 343; ir (potassium bromide): ν CO urea 1610, CO anhydride 1725.

Anal. Calcd. for $C_{17}H_{14}N_2O_6$: C, 59.65; H, 4.12; N, 8.18; O, 28.04. Found: C, 59.52; H, 4.12; N, 8.20; O, 27.98.

1,3-Diphenyl-1,3-bis(2'-ethoxy-1'-hydroxy-2'-oxoethyl)urea (**7b**).

A solution of **6** (520 mg, 2.4 mmoles) 550 mg (5.4 mmoles) of diphenylurea **3b** and 47.5 mg (0.25 mmole) of *p*-toluenesulfonic acid in toluene (40 ml) was heated to reflux during 4 hours by the use of a Dean-Stark apparatus. Water (30 ml) was then added and the resulting solution was extracted with ethyl acetate (3 x 20 ml). The combined organic layers were washed successively with 5% solution of sodium bicarbonate (40 ml), water (40 ml) and then dried over anhydrous sodium sulfate. After concentration under reduced pressure the residue was purified by flash-chromatography over silica gel (toluene) to afford **7b** as an oil, 713 mg (70%); Rf = 0.6 (toluene/ethyl acetate 75/25); ^{1}H nmr (deuteriochloroform): δ 1.26 (t, 6H, CH_3, J = 7 Hz), 1.63 (s, 2H, OH), 4.01 (dq, 2H, CH_2, J = 7 Hz and J = 8.6 Hz), 4.24 (dq, 2H, CH_2, J = 7 Hz and J = 8.6 Hz), 5.70 (s, 2H, CH), 7.20-7.73 (m, 10 H, H arom); ^{13}C nmr (deuteriochloroform): δ 15.3 (CH_3), 64.5 (CH_2), 85.5 (CH-OH), 121.1-129.7 (C arom), 152.1 (C=O urea), 166.3 (C=O ester).

Anal. Calcd. for $C_{21}H_{24}N_2O_7$: C, 60.56; H, 5.80; N, 6.72; O, 26.89. Found: C, 60.72; H, 5.81; N, 6.69; O, 26.81.

1,3-Bis(1-naphthylmethyl)-1-(2'-ethoxy-1'-hydroxy-2'-oxoethyl)urea (**8a**).

To a refluxing solution of 200 mg (0.58 mmole) of **3a** in toluene (20 ml) was added 132 mg (1.29 mmoles) of **6** and catalytic *p*-toluenesulfonic acid by the use of a Dean-Stark apparatus. The resulting mixture was heated to reflux for 3 hours then cooled to room temperature. Toluene was removed under reduced presure. Water was added and the aqueous layer was extracted with ethyl acetate (3 x 20 ml). The combined organic extracts were dried over anhydrous sodium sulfate. Evaporation of the solvent affored a yellow oil which was chromatographed over silica gel (toluene) to provide **8a**, 128 mg, (40%); Rf = 0.8 (toluene/ethyl acetate: 4/1); ^{1}H nmr (deuteriochloroform): δ 1.18 (t, 3H, CH_3, J = 6.9 Hz), 1.66 (s, 1H, OH), 3.37 (dq, 1H, CH_2 ester *anti*, J = 7 Hz and J = 8.6 Hz), 3.68 (dq, 1H, CH_2 ester *syn*, J = 7 Hz and J = 8.6 Hz), 4.62 (d, 1H, CH_2 naphth. *syn*, J = 15 Hz), 5.21 (dd, 2H, CH_2 naphth. *anti*, J = 15 Hz), 5.53 (d, 2H, CH_2 naphth. *syn*, J = 15 Hz), 7.25 (dd, 1H, CH, J = 7 Hz), 7.44-8.38 (m, 14 H, H arom); ^{13}C nmr (deuteriochloroform): δ 14.8 (CH_3), 40.3 (CH_2 naphth.), 41.7 (CH_2 naphth.), 62.5 (CH_2 ester), 82.3 (CH-OH), 123.3-129.3 (C arom), 155.0 (C=O urea), 169.5 (C=O ester).

Anal. Calcd. for $C_{27}H_{26}N_2O_4$: C, 73.28; H, 5.92, N, 6.33; O, 14.46. Found: C, 73.47; H, 5.93; N, 6.32; O, 14.44.

1,3 -Bis(1-methylnaphthyl)imidazoline-2,4,5-trione (**12a**).

To a warm solution of 30 mg (0.08 mmole) of **3a** in toluene (10 ml) was added 26 mg, (0.26 mmole) of triethylamine and 20 mg (0.16 mmole) of 4-dimethylaminopyridine. To the resulting mixture was added dropwise, at room temperature, 30 mg (0.22 mmole) of ethyl oxalyl chloride **11**. The mixture was stirred at room temperature for 3 hours. Water was then added and the aqueous layer was extracted with toluene (3 x 5 ml). The combined organic layers were washed successively with 5% solution of sodium bicarbonate (5 ml), 5% solution of citric acid (5 ml) and water (5 ml) and dried over sodium sulfate. After evaporation under reduced pressure, the residue give **12a**, 27 mg (76%) as a yellow product; Rf = 0.25 (toluene); ^{1}H nmr (deuteriochloroform): δ 5.22 (s, 4H, CH_2), 7.43-7.66 (m, 8H, H arom), 7.81-7.93 (m, 4H, H arom), 8.25-8.29 (d, 2H, H arom); ^{13}C nmr (deuteriochloroform): δ 45.9 (CH_2), 128.0-138.7 (C arom), 158.6 (C=O urea), 161.2 (C=O amide).

Anal. Calcd. for $C_{25}H_{18}N_2O_3$: C, 76.13; H, 4.59; N, 7.10; O, 12.16. Found: C, 76.30; H, 4.60; N, 7.09; O, 12.14.

1,3 -Diphenylimidazoline-2,4,5-trione (**12b**).

To a solution of 200 mg (0.94 mmole) of **3b** and 0.28 g (2.82 mmoles) of triethylamine in diethyl ether (30 ml) was added dropwise, at 0°, 0.25 ml (2.26 mmole) of compound **11** dissolved in diethyl ether (10 ml). The mixture was stirred at room temperature for 24 hours. Water (10 ml) was added and the aqueous layer was extracted with diethyl ether (2 x 10 ml). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by flash-chromatography (toluene/ethyl acetate: 4/1) to give **12b**, 200 mg (80%); ^{1}H nmr (deuteriochloroform): δ 7.62 (m, 10H, H arom), ^{13}C nmr (deuteriochloroform): δ 126.2-130.9 (C arom), 154.3 (C=O urea), 161.2 (C=O amide); ms: [M+H] = 267; ir (potassium bromide): ν CO urea 1578, CO amide 1613.

Anal. Calcd. for $C_{15}H_{10}N_2O_3$: C, 67.66; H, 3.78; N, 10.52; O, 18.02. Found: C, 67.41; H, 3.76; N, 10.48; O, 18.08.

3a,6a-*trans*-2,2-Dimethyl-4,6-dioxotetrahydro-4*H*-1,3-dioxolo[4,5-c]pyrrole-5-carboxamide (**14c**).

To absolute ethanol (15 ml), 600 mg (26.5 mmoles) of sodium was added portionwise. After 30 minutes 1 g (15.6 mmoles) of urea, dissolved in hot absolute ethanol (5 ml) was added. At 0°, 3.4 g (15.6 mmoles) of (-)dimethyl-2,3-*O*-isopropylidene-L-tartrate **13** was added dropwise. The reaction was refluxed for 30 hours. After evaporation of the solvent, water was added (50 ml) and neutralized to *p*H = 7 with a solution of 1*N* hydrochloric acid. The aqueous layer was extracted with ethyl acetate (3 x 15 ml), dried over sodium sulfate and concentrated under reduced pressure. Flash-chromatography (toluene/ethyl acetate: 92/8) yielded **14c**, 1.43 g (43%); ^{1}H nmr (deuteriochloroform): δ 1.48 (s, 3H, CH_3, isopropylidene), 1.54 (s, 3H, CH_3 isopropylidene), 4.91 (s, 2H, CH), 8.2 (br s., 2H, NH_2); ^{13}C nmr (deuteriochloroform): δ 25.9 (CH_3), 27.0 (CH_3), 76.4 (CH), 116.7 (C isopropylidene), 172.2 (C=O amide); ms: [M+H] = 215.

Anal. Calcd. for $C_8H_{10}N_2O_5$: C, 44.86; H, 4.70; N, 13.08; O, 37.35. Found: C, 44.68; H, 4.71; N, 13.11; O, 37.20.

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