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New synthesis of 1,2,3,6,7,11b-hexahydro-4*H*-pyrimido[6,1-*a*]isoquinolin-4-ones and 2,3,6,7,12,12b-hexahydropyrimido[1′,6′:1,2]pyrido[3,4-*b*]indol-4(1*H*)-ones

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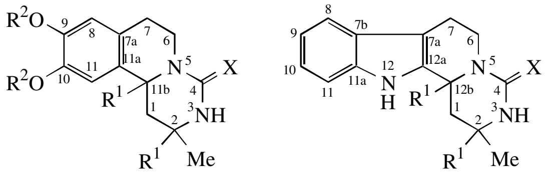
The title compounds were synthesised by the interaction of α,β-unsaturated carbonyl compounds with *N*-phenylethyl- and *N*-[2-(1*H*-indol-3-yl)ethyl]ureas.

Isoquinolines fused to pyrimidines are interesting as physiologically active compounds.[1] The pyrimido[1′,6′:1,2]pyrido[3,4-*b*]indol-4(1*H*)-one structure was found in the alkaloid elaeocapridine.[2] However, compounds from this class are difficult to synthesise. For example, methods for the preparation of 1,2,3,6,7,11b-hexahydro-4*H*-pyrimido[6,1-*a*]isoquinolin-4-ones **1** and **2** are multi-step syntheses,[3] whereas 2,3,6,7,12,12b-hexahydropyrimido[1′,6′:1,2]pyrido[3,4-*b*]indol-4(1*H*)-ones **3** are unknown.



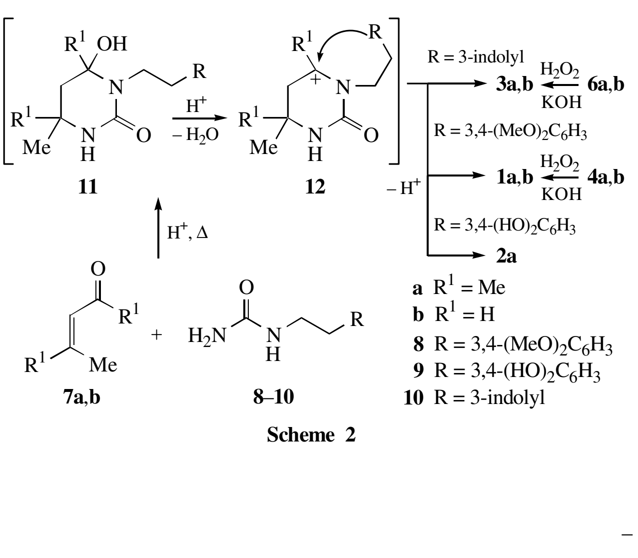
1, **2**, **4**, **5a**,**b** **3**, **6a**,**b**

1–**3** X = O
4–**6** X = S
1, **4** R^2 = Me
2, **5** R^2 = H
a R^1 = Me
b R^1 = H

Scheme 1

Intramolecular amidoalkylation of substituted heterocycle aminium ions is frequently used for preparing isoquinolines and β-carbolines fused with other heterocycles.[4] We found previously that 6-hydroxy-1-(3,4-dimethoxyphenethyl)- and 1-[2-(1*H*-indol-3-yl)ethyl]tetrahydro-2(1*H*)-pyrimidinethiones, synthesised by the interaction of 1,3-isothiocyanatocarbonyl compounds with [2-(3,4-dimethoxyphenyl)ethyl]amine or [2-(1*H*-indol-3-yl)ethyl]amine, cyclise in acid media to form compounds **4**–**6a**,**b**.[5] The oxygen analogues of these compounds, 6-hydroxytetrahydro-2(1*H*)-pyrimidin-2-ones **11**, can be synthesised from α,β-unsaturated carbonyl compounds and substituted ureas.[6] Inasmuch as such an interaction proceeds in acid media where hydroxypyrimidine **11** can form carbocation **12**, it is possible to expect cascade cyclisation to give compounds **1**–**3** (Scheme 2).

Therefore, heating mesityl oxide **7a** or 2-butenal **7b** with ureas **8**, **9** or **10** in ethanol gave compounds **1a**,**b**, **2a** and **3a**,**b**, respectively, in 63–94% yields (Scheme 2).[†] Compounds **1b** and **3b** are formed as a mixture of *cis*/*trans*-2,11b and *cis*/*trans*-2,12b isomers in a ratio of 3:2 or 5:8, respectively.



Scheme 2

The structure of compounds **1a**,**b**, **2a** and **3a**,**b** was confirmed by IR, ^{1}H and ^{13}C NMR spectra.[‡] Compounds **1a**,**b** and **3a**,**b** were synthesised by another method, the transformation of a thiourea fragment of pyrimidines **4a**,**b** and **6a**,**b**[5] by alkaline hydrogen peroxide to an urea fragment (Scheme 2).[§] The transformation of compound **5a** under the same conditions led to a mixture, which was difficult to separate.

The melting points of compounds **1a** and **3a** obtained by different methods are coincident. Compounds **1b** and **3b** synthesised from compounds **4b** and **6b** were obtained as isomer mixtures. The ratios between *cis*/*trans*-2,11b **1b** and *cis*/*trans*-2,12b **3b** isomers were 3:1 and 1:5, respectively.

The chemical shifts and couple constants of compounds **1a**,**b**, **2a** and **3a**,**b** in the ^{1}H and ^{13}C NMR spectra[‡] are consistent with published data for analogues.[3,5] The ^{1}H NMR spectra of

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[†] *Interaction of α,β-unsaturated carbonyl compounds* **7a**,**b** *and substituted ureas* **8**–**10** *(general procedure).* Two drops of conc. HCl were added to a solution of urea **8**, **9** or **10** (8.96 mmol) and α,β-unsaturated carbonyl compound **7** (17.9 mmol) in ethanol (7 ml), and the mixture was refluxed for an appropriate time. Upon cooling, the reaction mixture was neutralised by the addition of a 5% $NaHCO_3$ solution. The solvent was removed under reduced pressure, the residue recrystallised from an appropriate solvent or purified by chromatography.

[‡] ^{13}C NMR spectra were recorded at condition of *J*-modulation.

For **1a**: reaction completed in 3 h, yield 69% (83% when synthesised by oxidation of **4a**), mp 92–93 °C (CCl_4). ^{1}H NMR ($CDCl_3$) δ: 1.10 (s, 2-Me), 1.38 (s, 2-Me), 1.65 (s, 11b-Me), 2.06 (d, 1-H_a, *J* 13.8 Hz), 2.25 (d, 1-H_e, 13.8 Hz), 2.57 (m, 7-H_e, 12.3 Hz), 2.84–3.11 (m, 6-H_a, 7-H_a, *J* 12.3 Hz, *J* 12.1 Hz, *J* 12.0 Hz, *J* 12.1 Hz), 3.86 (s, 10-OMe), 3.88 (s, 9-OMe), 4.61–4.71 (m, 6-H_e, NH, *J* 12.0 Hz), 6.57 (s, 11-H), 6.61 (s, 8-H). ^{13}C NMR ($CDCl_3$) δ: 28.6 (11b-Me), 28.8 (C^7), 30.9 (2-Me), 32.4 (2-Me), 36.3 (C^6), 49.0 (C^2), 55.8 (9-OMe), 56.3 (10-OMe), 56.4 (C^{11b}), 56.6 (C^1), 108.6 (C^{11}), 111.8 (C^8), 126.1 (C^{7a}), 135.0 (C^{11a}), 147.6 (C^9, C^{10}), 155.6 (C=O). IR ($CHCl_3$, ν/cm^{-1}): 3420 (NH), 1650 (CO). Found (%): C, 67.22; H, 7.90; N, 9.21. Calc. for $C_{17}H_{24}N_2O_3$ (%): C, 67.08; H, 7.95; N, 9.20.

For **1b** (described[7] as a 1:1 mixture of diastereomers): reaction completed in 4 h, yield 63% (47% when synthesised by oxidation of **4b**), mp 185–187 °C (152–153 °C when synthesised by oxidation of **4b**) (AcOEt). ^{1}H NMR ($CDCl_3$) δ: 2.41 (m, 1-H_e, *J* 12.8 Hz, *J* 3.4 Hz, *J* 3.4 Hz), 2.59 (m, 7-H_e, *J* 13.7 Hz), 2.76–2.90 (m, 7-H_a, 6-H_a), 3.64–3.74 (m, 2-H), 3.87 (s, 9,10-OMe), 4.60–4.72 (m, 11b-H, 6-H_e, *J* 11.5 Hz, *J* 11.5 Hz, *J* 3.0 Hz), 6.62 (s, 11-H), 6.64 (s, 8-H); *cis*-isomer: 1.32 (d, 2-Me, *J* 6.4 Hz), 2.09 (m, 1-H_a), 5.99 (s, NH); *trans*-isomer: 1.23 (d, 2-Me, *J* 6.4 Hz), 1.53 (m, 1-H_a, *J* 12.8 Hz, *J* 12.8 Hz, *J* 11.5 Hz), 5.15 (s, NH). ^{13}C NMR ($CDCl_3$) δ: 39.6 (C^6), 55.8 (9-OMe), 56.1 (10-OMe), 108.5 (C^{11}), 111.6 (C^8), 127.4 (C^{7a}), 128.2 (C^{11a}), 147.6 (C^9, C^{10}); *cis*-isomer: 23.0 (2-Me), 28.7 (C^7), 36.1 (C^1), 43.5 (C^2), 50.5 (C^{11b}), 156.1 (C=O); *trans*-isomer: 21.9 (2-Me), 28.9 (C^7), 39.3 (C^1), 45.3 (C^2), 54.0 (C^{11b}), 155.9 (C=O). IR ($CHCl_3$, ν/cm^{-1}): 3450 (NH), 1650 (CO). Found (%): C, 65.13; H, 7.20; N, 10.16. Calc. for $C_{15}H_{20}N_2O_3$ (%): C, 65.20; H, 7.30; N, 10.14.

[§] *Synthesis of* **1** *and* **3a**,**b** *by the oxidation of* **4** *or* **6a**,**b** *(general procedure).* A 30% H_2O_2 solution (9.5 ml) was slowly added to a solution of **4** or **6** (9.56 mmol) and KOH (1.286 g, 23.0 mmol) in ethanol (50 ml) with such a rate that the temperature did not exceed 35–40 °C. After that the solution was stirred for 1.5 h, the solvent removed under reduced pressure, and the residue poured into water (100 ml). The crystals that formed were collected and recrystallised from an appropriate solvent.

compounds **1a**,**b**, **2a** and **3a**,**b** exhibit a high chemical shift (4.60–4.80 ppm) of the equatorial proton at C-6. This may be due to the deshielding effect of the urea group.

Thus, we found that the interaction of α,β-unsaturated carbonyl compounds **7a**,**b** with substituted ureas **8**, **9** and **10** proceeds as a cascade cyclisation with the formation of compounds **1**–**3**.

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For **2a**: reaction completed in 12 h, yield 77%, mp 137–138 °C (AcOEt). ^{1}H NMR (CDCl$_3$) δ: 0.95 (s, 2-Me), 1.24 (s, 2-Me), 1.48 (s, 11b-Me), 1.90 (d, 1-H$_a$, *J* 12.3 Hz), 2.16 (d, 1-H$_e$, *J* 12.3 Hz), 2.30–2.65 (m, 7-H$_e$, 7-H$_a$), 2.87 (m, 6-H$_a$), 4.32 (m, 6-H$_e$), 6.42 (s, 8,11-H), 6.60 (s, NH), 8.63 (s, 10-OH), 8.87 (s, 9-OH). IR (CHCl$_3$, ν/cm^{-1}): 3450 (NH), 3120 (OH), 1690 (CO). Found (%): C, 65.19; H, 7.25; N, 10.10. Calc. for $C_{15}H_{20}N_2O_3$ (%): C, 65.20; H, 7.30; N, 10.14.

For **3a**: reaction completed in 15 min, yield 87% (78% when synthesised by oxidation of **6a**), mp 276–277 °C (acetone). ^{1}H NMR ([^{2}H$_6$]DMSO) δ: 1.00 (s, 2-Me), 1.32 (s, 2-Me), 1.67 (s, 11b-Me), 2.22 (d, 1-H$_a$, *J* 13.8 Hz), 2.31 (d, 1-H$_e$, *J* 13.8 Hz), 2.61 (m, 7-H$_e$, J 15.2 Hz, *J* 4.2 Hz), 2.77 (m, 7-H$_a$, *J* 15.2 Hz, *J* 11.2 Hz, *J* 4.7 Hz), 3.13 (m, 6-H$_a$, *J* 13.7 Hz, *J* 11.2 Hz, *J* 4.2 Hz), 4.69 (dd, 6-H$_e$, *J* 13.7 Hz, *J* 4.7 Hz), 5.93 (s, NH), 6.97 (m, 10-H, *J* 7.1 Hz, *J* 7.1 Hz, *J* 1.0 Hz), 7.05 (m, 9-H, *J* 7.1 Hz, *J* 7.1 Hz, *J* 1.0 Hz), 7.30 (dd, 11-H, *J* 7.1 Hz, *J* 1.0 Hz), 7.39 (dd, 8-H, *J* 7.1 Hz, *J* 1.0 Hz), 10.59 (s, N^{12}H). ^{13}C NMR ([^{2}H$_6$]DMSO) δ: 20.9 (C^7), 27.6 (11b-Me), 30.4 (2-Me), 30.6 (2-Me), 36.7 (C^6), 46.2 (C^2), 48.3 (C^1), 54.2 (C^{12b}), 105.8 (C^{7a}), 111.0 (C^{11}), 117.7 (C^9), 118.4 (C^8), 120.7 (C^{10}), 126.6 (C^{7b}), 135.8 (C^{11a}), 139.8 (C^{12a}), 155.5 (C=O). IR (CHCl$_3$, ν/cm^{-1}): 3430, 3500 (NH), 1610 (CO). Found (%): C, 72.18; H, 7.47; N, 14.72. Calc. for $C_{17}H_{21}N_3O$ (%): C, 72.06; H, 7.47; N, 14.83.

For **3b**: reaction mixture was heated to boiling, yield 94% (73% when synthesised by oxidation of **6b**), mp 129–131 °C (160–161 °C when synthesised by oxidation of **6b**), purified by chromatography on a silica gel (CHCl$_3$:AcOEt:EtOH, 6:3:1). ^{1}H NMR (CDCl$_3$) δ: 2.47 (d, 7-H$_e$, *J* 13.4 Hz), 2.70 (dd, 7-H$_a$, *J* 13.4 Hz, *J* 11.4 Hz), 2.91 (dd, 6-H$_a$, *J* 13.2 Hz, *J* 11.4 Hz), 3.47 (m, 2-H), 4.66–4.80 (m, 11b-H, 6-H$_e$), 7.08 (dd, 10-H, *J* 6.3 Hz, *J* 7.5 Hz), 7.14 (dd, 9-H, *J* 6.3 Hz, *J* 7.3 Hz), 7.32 (d, 11-H, *J* 7.5 Hz), 7.46 (d, 8-H, *J* 7.3 Hz), 9.07 (s, N^{12}H); *cis*-isomer: 1.21 (d, 2-Me, *J* 6.3 Hz), 2.03–2.20 (m, 1-H$_a$, 1-H$_e$), 5.32 (s, NH); *trans*-isomer: 1.13 (d, 2-Me, *J* 6.3 Hz), 1.54 (m, 1-H$_a$, *J* 12.5 Hz, *J* 1.6 Hz, *J* 10.8 Hz), 2.05–2.16 (m, 1-H$_e$), 5.13 (s, NH). ^{13}C NMR (CDCl$_3$) δ: 20.2 (C^7), 39.9 (C^6), 107.4 (C^{7a}), 110.3 (C^{11}), 116.8 (C^9), 117.8 (C^8), 120.1 (C^{10}), 126.0 (C^{7b}), 133.3 (C^{11a}), 135.5 (C^{12a}); *cis*-isomer: 21.5 (2-Me), 32.6 (C^1), 42.3 (C^2), 47.9 (C^{12b}), 154.8 (C=O); *trans*-isomer: 20.8 (2-Me), 35.8 (C^1), 44.1 (C^2), 51.2 (C^{12b}), 155.0 (C=O). IR (CHCl$_3$, ν/cm^{-1}): 3430, 3490 (NH), 1620 (CO). Found (%): C, 70.68; H, 6.75; N, 16.47. Calc. for $C_{15}H_{17}N_3O$ (%): C, 70.56; H, 6.71; N, 16.46.