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Regioselectivity in The Reductive Formation of Dihydro-5-halo-2(1*H*)-pyrimidinones

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5-Chloro-2(1*H*)-pyrimidinones are reduced by lithium tri-*tert*-butoxyaluminum hydride to dihydropyrimidinones. Pyrimidines with a substituent capable of conjugation gave the dihydro isomer which has its double bond in conjugation with this substituent. In the adduct formation between the 2(1*H*)-pyrimidinone and the lithium enolate of acetophenone, the carbon-carbon bond formation was at C-4. The adducts were easily dehydrogenated to phenacylidene derivatives which have been shown by X-ray analysis and spectroscopy to have the (*Z*)-configuration involving strong intramolecular hydrogen bonding.

Dihydropyrimidines may be incorporated in RNA.[1] Syntheses of dihydropyrimidines are thus of interest for the studies of dihydropyrimidines as potential pyrimidine agonists or antagonists. This paper describes such work related to our interest in 2(1*H*)-pyrimidinone inhibitors of cell proliferation.[2]

Some dihydro-2(1*H*)-pyrimidinones have been prepared by cyclocondensation reactions.[3] Reports on the reduction of the fully conjugated pyrimidine, show that a C–N double bond may initially be reduced,[4] whereas in uracils it is the 5,6-dihydro compound which is the initial product.[5] 2(1*H*)-Pyrimidinone and its *N*-methyl derivative have been reduced to the 3,6-dihydro derivative by catalytic hydrogenation over platinum.[4a] Deactivated Raney-nickel desulfurization of 5,6-dihydro-4-thiouracils is an alternative route to such compounds.[6] With sodium borohydride or lithium aluminum hydride (LAH) reduction of 1,4,6-trisubstituted-2(1*H*)-pyrimidinones, either 3,4- or 3,6-dihydro or 3,4,5,6-tetrahydro derivatives or mixtures thereof are formed.[4b] Lithium borohydride reduction likewise gave a dihydro derivative.[4c]

The π-electron deficiency in the 2(1*H*)-pyrimidinone system is increased by a 5-chloro substituent, and the compounds *1* are therefore readily reduced. With LAH *1a* gave several products (TLC). Catalytic hydrogenation of *1a* over platinum gave the tetrahydro derivative *6*; the hydrogenolysis of the chlorine substituent has its analogy in related work.[7] Hydrogenolysis and overreduction could be avoided by the use of lithium tri-*tert*-butoxyaluminum hydride which gave dihydropyrimidines. The parent compound *1b*, which does not contain the 5-chloro substituent, did not react with this reagent under the conditions used for the 5-chloro analogous. From *1a* the 3,6- and 3,4-dihydro isomers *2a* and *3a* were formed in the ratio *ca.* 9:1, respectively (^{1}H NMR) and can be separated by chromatography. The reaction requires a few minutes at room temperature. The 4-carboxy derivative *1c* is more reactive; at −78 °C the pyrimidine ring was reduced in preference to

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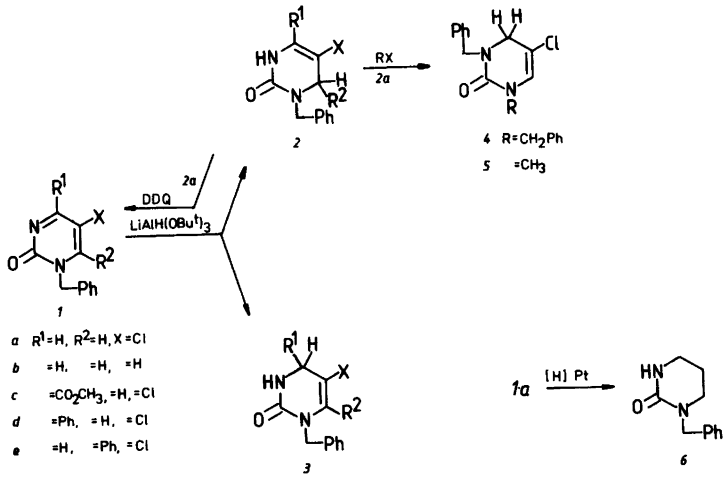


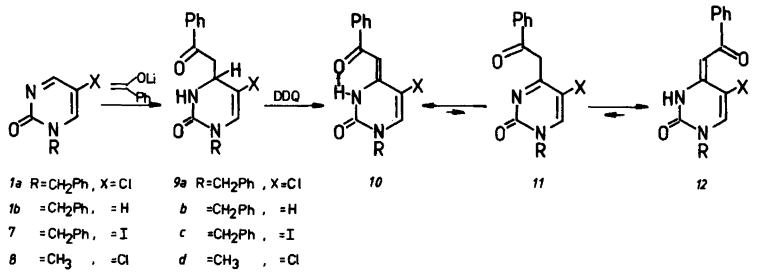
Scheme 1.

the ester group, the product being the 3,6-dihydro derivative *2c*. The selective formation of this dihydro isomer is attributed to conjugation of the double bond with the ester group as well as to non-bonded interaction between the ester group and the reducing agent preventing attack at C-4. For the same reasons, presumably, the 4-phenyl compound *1d* was reduced to the 3,6-dihydro derivative *2d*, whereas the 6-phenyl compound *1e* furnished the 3,4-dihydro derivative *3e*.

The structures which were assigned to the dihydro derivatives from *1d* and *1e*, have been verified by comparisons with authentic specimens. The structures of the dihydro isomers from *1a* were assigned by ^{1}H NMR spectra. The major isomer exhibited a broad resonance at 7.60 ppm readily assignable to the amino proton. A resonance at 6.19 ppm assignable to the ring methine proton consisted of a doublet of triplets (J 5.08 and J 1.37 Hz). It was shown by proton decoupling experiments that the doublet splitting was due to coupling to the amino proton (J *ca.* 5 Hz) whilst the triplet splitting was due to coupling with the ring methylene protons which appeared as a doublet at 3.89 ppm (J 1.37 Hz). The size of the two couplings shows that the compound is the 3,6-dihydro isomer *2a*. A characteristic feature is the location of the 3-amino proton; in the 3,6-dihydro derivatives *2a*, *2c* and *2d* the shifts were at 7.6, 7.1 and 6.9 ppm, respectively, whereas the shifts for the 3,4-dihydro derivatives *3a* and *3e* were at 6.0 and 5.8 ppm, respectively. This finding fits into the pattern previously observed for other 3,4- and 3,6-dihydro-2(1*H*)-pyrimidinones in which case the shift differences between the 3,4 and 3,6-dihydro isomer series were *ca.* 2 units.[3a] The resonances of the ring methylene protons in the 3,6- and the 3,4-dihydro isomers *2a* and *3a*, however, were at *ca.* 3.9 ppm as in the dialkylated derivatives *4* and *5*.

Carbon nucleophiles can also be used in adduct formation with 2(1*H*)-pyrimidinones whereby the corresponding dihydro derivatives can be obtained. For this purpose the lithium enolate of acetophenone was investigated.

The lithium enolate of acetophenone reacts rapidly at 0 °C with the 5-chloro-2(1*H*)-pyrimidinones *1a* and *8*. The phenacyl group is introduced at C-4, the product being the 3,4-dihydro derivatives *9a* and *9d* as verified for the dehydrogenated derivatives *10*. The 5-iodopyrimidinone *7* did not form an adduct with the enolate presumably for steric reasons.



Scheme 2.

The compound *1b*, which does not contain a 5-halogen substituent, reacted in the same regioselective manner as its 5-chloro homologue *1a*. The adducts were very readily dehydrogenated to the fully conjugated compounds *11* which, however, exist as the tautomers *10* which have an exocyclic double bond conjugated with the carbonyl group. From the reaction of *1a* and *8* with the lithium enolate, a mixture of *9* and its dehydrogenated analogue *10* was obtained. From the reaction of *1b* only the dehydrogenated product *10b* was isolated. Acetophenone did not seem to be involved in the redox process since its reduction product 1-phenylethanol was not seen (GLC–MS).

The adducts *9* are rapidly dehydrogenated to *10* by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). The phenacyl group promotes this reaction since in its absence such as in the case of *2a*, prolonged heating with DDQ was required for the regeneration of the fully conjugated ring *1a*.

The structure of the compound drawn as *10d* has been verified by X-ray analysis.[8] Hence *10d* serves as a reference compound for the comparison of spectroscopic data in the assignment of structures to the other compounds. In *10d* the pyrimidine ring and the phenacylidene side-chain are approximately coplanar, the torsional angle being within 5° except for the phenyl ring which was twisted 30° with respect to this plane. *10d* has the (*Z*)-configuration. Rather strong intramolecular hydrogen bonding between the N-3 proton and the carbonyl oxygen in the side-chain results in a six-membered pseudo-ring. The H···O distance is 1.85 Å and the N–H···O angle is as large as 139° which makes the interaction geometrically favourable.

The *N*-benzyl derivative is also assigned the (*Z*)-configuration *10a* for spectroscopic reasons. Compound *10b*, which is without the 5-halogen atom, however, shows some spectroscopic discrepancies. In IR the exocyclic oxo group in *10a* and *10b* was at 1693 and 1671 cm^{-1} whereas in ^1H NMR (200 MHz) the exocyclic olefinic proton was at 6.24 and 5.87 ppm, respectively. The NH proton was at low field, *viz.* at 13.2 and 13.1 ppm for *10a* and *10b* respectively, which is consistent with strong hydrogen bonding. This can be compared with the weaker hydrogen bonding expected in the dihydro derivatives *9a* and *9d* where the NH-absorption was in the region 5.6–5.7 ppm. Furthermore, the position of the NH absorption of either *10a* or *10b* was independent of the concentration of the compound in support of intramolecular hydrogen bonding in a pseudo six-membered ring. Additional evidence for the (*Z*)-configuration (*10b*) comes from the lack of long range coupling between H-6 and the exocyclic olefinic proton as would have been expected for the zig-zag pattern present in the (*E*)-configuration *12b*. Finally, in ^{13}C NMR the long range coupling in *10b* between the exocyclic olefinic proton and C-5 was the same (*J* 5 Hz) as for *10a*.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded at 60 MHz unless otherwise stated. The mass spectra which were obtained by electron bombardment are presented as MS(EI) [70 eV; *m/z* (rel.int.)], and by chemical ionization using isobutane, as MS(CI) [*m/z* (rel.int.)].

1-Benzyl-5-chloro-4-methoxycarbonyl-2(1H)-pyrimidinone 1c. Benzyl bromide (5.71 g, 3.34 mmol) was added to a mixture from 5-chloro-4-methoxycarbonyl-2(1*H*)-pyrimidinone (6.00 g, 3.18 mmol) and potassium *tert*-butoxide (3.75 g, 3.34 mmol) in dry DMF (100 ml) and the resulting mixture stirred at room temperature for 8 h. The solvent was then distilled off at 1 mmHg, the residue extracted with chloroform and the chloroform solution filtered through alumina (neutral, activity III). Evaporation of the eluate and recrystallization of the residue from ethyl acetate gave the product; yield 5.58 g (63 %), m.p. 106–107 °C. Anal. $C_{13}H_{11}ClN_2O_3$: C,H. ^{1}H NMR ($CDCl_3$): δ 3.98 (OCH_3), 5.17 (CH_2), 7.43 (Ph), 8.03 (H-6). IR (KBr): 1649 and 1739 cm^{-1} (CO). MS(CI) 281/279 (39/100, M+H), 221 (2.0), 189 (2.0), 91 (23).

3,6-Dihydro- and 3,4-dihydro-1-benzyl-5-chloro-2(H)-pyrimidinone, 2a *and* 3a. Lithium tri-*tert*-butoxyaluminum hydride (20.34 g, 80 mmol) was added gradually with stirring at room temperature during 15 min to a solution of 1-benzyl-5-chloro-2-(1*H*)-pyrimidinone (8.82 g, 40 mmol) in dry THF (250 ml). The mixture was stirred at room temperature for 15 min before water (100 ml) was added and the pH adjusted to *ca.* 7 by 1 M HCl. Most of the solvent was then evaporated, the residual aqueous suspension extracted with ether (4×100 ml), the combined extracts washed with aqueous NH_4Cl (2×50 ml) and the dried ($MgSO_4$) solution evaporated. The product (8.10 g, 91 %) was a mixture of *2a* and *3a* in the ratio 84:16 by ^{1}H NMR estimation. One recrystallization from chloroform gave the pure 3,6-dihydro isomer *2a*; yield 6.15 g (69 %), m.p. 117–118.5 °C. Anal. $C_{11}H_{11}ClN_2O$: C.H. ^{1}H NMR (100 MHz; $CDCl_3$): 3.89 (2H-6, d, J 1.37 Hz), 4.53 (CH_2Ph,s), 6.19 (H-4, d of t, $J_{3,4}$ 5.08 (d), $J_{4,6}$ 1.37 (t)), 7.22 (Ph,s), 7.60 (NH, broad, $J_{3,4}$ *ca* 5). ^{13}C NMR ($CDCl_3$): δ 50.5 (CH_2Ph, t, J_{CH} 138 Hz), 50.8 (CH_2-6, t, J_{CH} 145 Hz 102.9 (C-5, s), 122.8 (C-4, d, J_{CH} 154 Hz), 126–136 (Ph), 153.3 (C-2, s). IR (CCl_4): 1665 cm^{-1} (CO). MS(EI): 224/222 (2/7,M), 223(2), 221 (2), 220 (7), 132 (10), 131 (77), 91 (100). MS(CI): 225/223 (19/60, M+H), 224(12), 222 (14), 187 (5), 145 (13), 133 (24), 131 (74) 132 (16), 91 (100).

For the isolation of the 3,4-dihydro isomer *3a* the filtrate after removal of *2a* was evaporated, the residue dissolved in chloroform and the solution chromatographed on an alumina column (neutral, activity I) using chloroform; *3a* was eluated before *2a*. *3a* had m.p. 152 °C ($CHCl_3$). Anal. $C_{11}H_{11}ClN_2O$: C,H ^{1}H NMR ($CDCl_3$): δ 4.10 (2H-4), 4.60 (CH_2Ph, s), 6.00 (NH, broad) 6.10 (H-6, t, $J_{4,6}$ 1.0 Hz), 7.37 (Ph). IR (CCl_4): 1670 cm^{-1} (CO). MS(EI): 224/222 (6/19, M), 223 (3), 221 (1), 187 (2), 92 (8), 91 (100).

1-Benzyl-5-chloro-3,6-dihydro-4-methoxycarbonyl-2(1H)-pyrimidinone 2c. Lithium tri-*tert*-butoxyaluminum hydride (0.92 g, 3.62 mmol) was slowly added with stirring to a solution of 1-benzyl-5-chloro-4-methoxycarbonyl-2(1*H*)-pyrimidinone (0.50 g, 1.79 mmol) in dry THF (75 ml) at ÷75 °C. The mixture was stirred at this temperature for another 30 min and then allowed to reach ÷5 °C before the reaction was stopped by addition of dilute HCl to pH *ca.* 3. Most of the THF was then evaporated, the remaining aqueous mixture extracted with ether (3×100 ml), and the washed (2×50 ml) and dried ($MgSO_4$) ether solution evaporated to furnish the crystalline *2c*; yield 0.44 g (87 %), m.p. 101 °C (EtOAc). Anal. $C_{13}H_{13}ClN_2O_3$: C,H. ^{1}H NMR ($CDCl_3$): δ 3.88 (OCH_3), 4.00 (2H-6, s) 4.57 (CH_2Ph), 7.1 (NH, broad), 7.37 (Ph). IR (KBr): 1652 and 1736 cm^{-1} (CO). MS(CI): 283/281 (35/100, M+H), 284 (5), 282 (17), 248 (4), 247 (8), 191 (2) 189 (6.0), 150 (3), 148 (8), 91 (14).

1-Benzyl-5-chloro-3,6-dihydro-4-phenyl-2(1H)-pyrimidinone 2d was prepared from 1-benzyl-5-chloro-4-phenyl-2(1*H*)-pyrimidinone (50 mg, 0.169 mmol) and lithium tri-*tert*-butoxyaluminum hydride (90 mg, 0.337 mmol) in dry THF (50 ml). The reaction was run at room temperature for 30 min and the mixture worked up as for *2c* above; yield 40 mg (79 %), m.p. 164 °C (EtOAc). Anal. $C_{17}H_{15}ClN_2O$: C,H. ^{1}H NMR ($CDCl_3$): δ 3.96 (2H-6, s), 4.47 (CH_2Ph), 6.93 (NH, broad), 7.30 and 7.37 (2 Ph). IR (KBr): 1639 cm^{-1} (CO). MS(Cl): 301/299 (25/100, M+H), 302 (4), 300 (18), 265 (8), 263 (23), 209 (6), 207 (21), 166 (10), 91 (42).

1-Benzyl-5-chloro-3,4-dihydro-6-phenyl-2(1H)-pyrimidinone 3e was prepared from 1-

benzyl-5-chloro-6-phenyl-2(1*H*)-pyrimidinone (50 mg, 0.169 mmol) and lithium tri-*tert*-butoxyaluminum hydride (90 mg, 0.337 mmol) in dry THF (50 ml). The reaction was run at room temperature for 30 min and the mixture worked up as for *2c* above; yield 35 mg (69 %) of a non-crystalline material. Anal. $C_{17}H_{15}ClN_2O$: C,H. ^{1}H NMR ($CDCl_3$): δ 4.23 (2H-4, s), 4.53 (CH_2Ph), 5.8 (NH, broad), 7.0–7.2 (2Ph). IR (KBr): 1685 cm^{-1} (CO). MS(CI): 301/299(16/100, M+H), 302 (4), 300 (22), 267 (12), 206 (12), 91 (70).

Dehydrogenation of 2a *with regeneration of* 1a. A solution of 1-benzyl-5-chloro-3,6-dihydro-2(1*H*)-pyrimidinone (0.10 g, 0.45 mmol) and DDQ (0.10 g, 0.45 mmol) in dioxan (40 ml) was heated under reflux for 24 h. The solution was then evaporated, the residue extracted with chloroform, the chloroform solution shaken with 1 M NaOH (10 ml) and with water, the dried ($MgSO_4$) solution evaporated and an ethyl acetate solution of the residue filtered through a column of silica gel; yield 50 mg (48 %), Lit.[9]

*5-Chloro-1,3-dibenzyl-3,4-dihydro-2(1*H*)-pyrimidinone* 4. Benzyl bromide (0.16 g, 0.95 mmol) was added to a solution which had been prepared from 1-benzyl-5-chloro-3,6-dihydro-2(1*H*)-pyrimidinone (0.20 g, 0.89 mmol) and sodium hydride (0.022 g, 0.92 mmol) in dry DMF (10 ml), and the mixture stirred at room temperature for 5 h. The mixture was then diluted with water, weakly acidified, extracted with ether (2×50 ml) and the washed and dried ($MgSO_4$) ether solution evaporated. The product was a non-crystalline material: yield 0.24 g (86 %). Anal. $C_{18}H_{17}ClN_2O$: C,H. ^{1}H NMR ($CDCl_3$): δ 3.83 (2H-4), 4.48 (CH_2Ph), 4.58 (CH_2Ph), 6.00 (H-6), 7.15 (2 Ph), MS(EI): 314/312 (1/3, M), 223 (3), 221 (6), 132 (3), 91 (100).

*3-Benzyl-5-chloro-3,4-dihydro-1-methyl-2(1*H*)-pyrimidinone* 5 was prepared as above in 85 % yield using methyl iodide. The product was a non-crystalline material. Anal. $C_{12}H_{13}ClN_2O$: C,H. ^{1}H NMR ($CDCl_3$): δ 3.07 (CH_3), 3.88 (2H-4), 4.55 (CH_2Ph), 6.03 (H-6), 7.20 (Ph). MS(EI): 238/236 (3/9, M), 147 (19), 145 (57), 132 (8), 92 (14), 91 (100).

*1-Benzyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone 6.* Platinum dioxide (0.20 g) was added to a solution of 1-benzyl-5-chloro-2-(1*H*)-pyrimidinone (3.31 g, 15 mmol) in ethanol (150 ml) and the mixture hydrogenated at 40 lbs/sq. inch for 2 h. The catalyst was then removed by filtration, the filtrate evaporated and the residue crystallized from dilute methanol; yield 2.66 g (93 %), m.p. 161 °C. Anal. $C_{12}H_{14}N_2O$: C,H. ^{1}H NMR ($CDCl_3$): δ 1.8 (2H-5), 3.2 (2H-4, 2H-6), 4.5 (CH_2Ph), 7.2 (Ph). IR (CCl_4): 1670 cm^{-1} (CO). MS(EI): 190 (59, M), 186 (10), 161 (14), 105 (15), 104 (34), 91 (100).

*1-Benzyl-5-chloro-3,4-dihydro-4-phenacyl-2(1*H*)-pyrimidinone* 9a. Acetophenone (6.00 g, 50 mmol) was added with stirring to a solution of LDA (43 mmol) in hexane-toluene (1:1; 70 ml) at 0 °C. The volume of the solution was reduced to *ca.* 20 ml at reduced pressure before 1-benzyl-5-chloro-2(1*H*)-pyrimidinone (5.51 g, 25 mmol) was added gradually with stirring at 0 °C. The mixture was stirred for 1 h at this temperature and allowed to reach room temperature. The mixture was then diluted, weakly acidified with HCl, and extracted with ether (3×100 ml). The ether was shaken with saturated aqueous sodium bicarbonate and washed with water, the dried ($MgSO_4$) solution evaporated and the acetophenone in the product removed by heating at reduced pressure. The residue was dissolved in ethyl acetate from which *9a* crystallized in 40 % yield (3.41 g). A second crop was obtained by evaporation of the filtrate and chromatography of the residue on a silica gel column (0.06–0.20 mm; 600 g) using ethyl acetate for eluation. The product first eluated was *9a*; yield 1.23 g (14 %). The second product was the dehydrogenated material *10a* as described below; yield 1.15 g (14 %).

Compound 9a. Total yield 54 %, m.p. 138–139 °C (EtOAc). Anal. $C_{19}H_{17}ClN_2O$: C,H. ^{1}H NMR ($CDCl_3$; 98 MHz): δ 3.29 and 3.56 (CH_2CO, AB, J 18 Hz), 4.59 (CH_2Ph, s), 4.72 (H-4), 5.74 (NH), 6.16 (H-6, s), 7.2–8.1 (2 Ph). IR (CCl_4): 1685 and 1690 cm^{-1} (CO). MS(EI): 342/340 (0.5/1.5, M), 223 (4), 221 (14), 220 (51), 219 (9), 105 (36), 91 (100). MS(CI): 343/341 (0.7/3.8, M+H), 342/340 (1/3), 339 (7), 325 (7), 313 (27), 312 (17), 311 (79), 223 (61), 222 (48), 221 (100).

*5-Chloro-3,4-dihydro-1-methyl-4-phenacyl-2(1*H*)-pyrimidinone* 9d was prepared as above from 5-chloro-1-methyl-2(1*H*)-pyrimidinone (9 mmol) and the equivalent amount of lithium enolate of acetophenone. The crude product from the reaction was dissolved in ethyl acetate from which the dehydrogenated product *10d* crystallized out in 50 % yield. Physical data are given below. The title compound was isolated by evaporation of the filtrate and

chromatography on silica gel using ethyl acetate for eluation as above. The first product eluated was *9d* followed by a second crop of the dehydrogenated derivative *10d* (16 %). The yield of *9d* was 12 %, m.p. 148–149 °C (EtOAc). Anal. $C_{19}H_{13}ClN_2O_2$: C,H. ^{1}H NMR (98 MHz, $CDCl_3$): δ 3.02 (CH_3), 3.31 and 3.57 (CH_2CO, AB, J 18 Hz), 4.72 (H-4), 5.61 (NH), 6.16 (H-6, s), 7.5–7.9 (Ph). IR (KBr): 1685 and 1690 cm^{-1} (CO). MS(EI): 266/264 (1.5/4.5), 229 (2), 147 (26), 146 (15), 145 (85), 144 (32), 120 (24), 116 (19), 105 (100). MS(CI): 267/265 (2/7, M+H), 266/264 (2/7), 263 (6), 147 (32), 145 (100).

*(Z)-1-Benzyl-5-chloro-4*H*-4-phenacylidene-2(1*H*)-pyrimidinone* 10a DDQ (0.35 g, 1.5 mmol) was added to a solution of 1-benzyl-5-chloro-3,4-dihydro-4-phenacyl-2(1*H*)-pyrimidinone (0.50 g, 1.5 mmol) in benzene (50 ml) and the mixture stirred at room temperature for 1 h before the insoluble material was filtered off. The solid was washed with benzene, the filtrate and benzene washings combined and concentrated to *ca.* 10 ml before the solution was chromatographed on a short alumina column (4 cm; neutral, activity II). The compound *10a* was eluated with chloroform; yield 0.47 g (95 %), m.p. 161 °C (EtOAc). Anal. $C_{19}H_{15}ClN_2O$: C,H. ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.89 (CH_2 Ph), 6.24 (=CH–CO, s), 7.02 (H-6, s), 7.2–8.0 (2 Ph), 13.24 (NH). ^{13}C NMR ($CDCl_3$): δ 51.7 (CH_2Ph), 89.7 (=*C*HCO), 107.3 (C-5, $J_{C,H_{viz.}}$ 5.0 Hz), 127.5–135.1 and 139.1 (2 Ph), 136.4 (H-6), 147.9 (C-2), 149.6 (C-4), 190.5 (=CHCO). IR ($CDCl_3$): 1631 and 1693 cm^{-1} (CO). MS(EI): 340/338 (5/16, M), 303 (24), 105 (9), 92 (7), 91 (100). MS(CI): 342/340 (5/32), 341/339 (31/95, M+H), 338 (26), 305 (16), 303 (22), 93 (76), 92 (33), 91 (100).

*(Z)-1-Benzyl-4*H*-4-phenacylidene-2(1*H*)-pyrimidinone* 10b. Acetophenone (1.61 g, 13.4 mmol) was added to a solution of LDA (13.4 mmol) in dry hexane (20 ml), toluene (20 ml) and THF (40 ml) at 0 °C. Subsequently 1-benzyl-2(1*H*)-pyrimidinone (2.50 g, 13.4 mmol) was added gradually with stirring to the enolate solution at 0 °C, and the stirring continued for 1 h at this temperature before the mixture was allowed to reach room temperature.

Water and HCl were then added to neutral pH, most of the organic solvents removed by evaporation, the aqueous suspension extracted with ether (4×100 ml) and the washed and dried ($MgSO_4$) ether solution evaporated to furnish the product; yield 3.43 g (84 %), m.p. 206 °C (EtOAc): Anal. $C_{19}H_{16}N_2O_2$: C,H. ^{1}H NMR (200 MHz; $CDCl_3$): δ 4.88 (CH_2Ph), 5.70 (H-5,d, $J_{5,6}$ 7.5 Hz, $J_{5,NH}$ 1,9 Hz), 5.87 (=CHCO, s), 6.83 (H-6, d, J 7.5 Hz), 7.2–8.0 (2 Ph), 13.09 (NH). ^{13}C NMR ($CDCl_3$): δ 51.4 (CH_2Ph), 91.1 (=*C*H CO), 102.8 (C-5) $J_{C,H\ viz.}$ 4.9 Hz), 127.3–135.7) and 139.4 (2 Ph), 138.8 (C-6), 148.9 (C-2), 152.8 (C-4), 190.0 (=CH–*C*O). IR (KBr): 1642 and 1671 cm^{-1} (CO). MS(EI): 304 (43, M), 303 (11), 227 (7), 213 (15), 105 (10), 91 (100).

*(Z)-5-Chloro-1-methyl-4*H*-4-phenacylidene-2(1*H*)-pyrimidinone 10*d was the major product (62 %) in the acetophenone lithium enolate addition reaction to *8* as described in the preparation of *9d*. The compound *10d* was also prepared from 5-chloro-3,4-dihydro-1-methyl-4-phenacyl-2(1*H*)-pyrimidinone (3.8 mmol) and DDQ as described for *10a* above. The yield was 80 %, m.p. 180–182 °C (EtOAc). Anal. $C_{19}H_{11}ClN_2O_2$: C,H. ^{1}H NMR ($CDCl_3$): δ 3.35 (CH_3), 6.21 (=CHCO, s) 7.04 H-6,s), 7.5–7.6 (Ph), 13.25 (NH). ^{13}C NMR (50.21 MHz); $CDCl_3$): 51.7 (CH_3), 89.7 (=*C*HCO), 107.2 (C-5), 127.5–135.1 and 139.2 (2 Ph), 136.3 (C-6), 147.9 (C-2), 149.9 (C-4), 190.5 (=CH*C*O). IR (KBr): 1630 and 1683 cm^{-1} (CO). MS(EI): 264/262 (14/43, M), 263/261 (11/17), 228 (29), 227 (100), 187 (10), 185 (31). MS(CI): 266/264 (4/23), 265/263 (33/100, M+H), 262 (27), 227 (30), 105 (16).

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