Di-π-methane Rearrangement of 4-Heteroaryl-1,4(or 3,4)-dihydropyrimidines [1]

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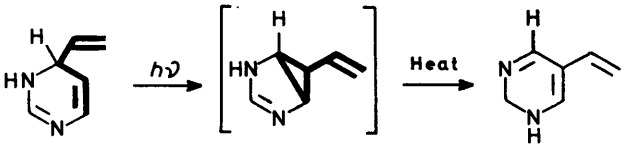
Several 4-R-1,4(or 3,4)-dihydropyrimidines (R = 2- or 3-thienyl, 2-furyl, 1-methylpyrrol-2-yl, and 3-pyridyl), containing heteroaryl vinyl methane units were shown to undergo photochemical rearrangement into 5-R-1,2(or 2,3)-dihydropyrimidines. These compounds were oxidized to yield 5-heteroarylpyrimidines. The chemical yields of the photorearrangement were found to be strongly dependent on the nature of the heteroaryl group.

THE reaction of organo-lithium compounds with pyrimidine is a convenient method for introducing substituents into the pyrimidine ring in the 4(or 6)- and sometimes in the 2-position.[2,3] In pyrimidine position 5 is inert for nucleophilic attack and 5-substituted pyrimidines cannot be prepared by this method. We recently reported the photochemical rearrangement of 4-phenyl-, 4-isobutenyl-, and 4-(phenylethynyl)-1,4(or 3,4)-dihydropyrimidines, obtained from reactions of pyrimidine with organo-lithium compounds and subsequent hydrolysis, into the corresponding 5-substituted 1,2(or 2,3)-dihydropyrimidines, which, on oxidation, gave 5-substituted pyrimidines.[1a] Evidence was presented that this photochemical isomerization involves a di-π-methane rearrangement. The di-π-methane unit is composed of the C(6)–C(5) double bond, the saturated carbon atom C(4) of the heterocyclic ring, and the π-bond in the α-position of the 4-substituent (heavy bonds in Scheme 1).



SCHEME 1

The course of this rearrangement thus seems to be determined by the presence of a π-bond in the 4-substituent of the dihydropyrimidine. Since these reactions led to a new preparation of 5-substituted pyrimidines, we have extended our investigations to a study of the rearrangement of 4-heteroaryl-1,4(or 3,4)-dihydropyrimidines. To our knowledge, di-π-methane rearrangements in which one of the double bonds is part of a heteroaromatic system have not been reported.

Formation of the 4-Heteroaryl-1,4(or 3,4)-dihydropyrimidines (3).—Reaction of a solution of the appropriate heteroaryl-lithium compound in ether or hexane at 0 °C with pyrimidine (1) and subsequent hydrolysis afforded the required 4-substituted 1,4(or 3,4)-dihydropyrimidines (3).[2] However, in the reactions of 2-furyl- and 3-pyridyl-lithium with (1) 2-substituted 1,2-(or 2,3)-dihydropyrimidines (2) were formed as well. The addition of 2-furyl-lithium into the 2-position of (1) could be suppressed completely by performing the reaction in tetrahydrofuran (THF) at 0 °C. The formation of 2-(3-pyridyl)-1,2(or 2,3)-dihydropyrimidine (2e) from (1) and 3-pyridyl-lithium could be minimized by performing the reaction in ether at −70 °C. The dihydropyrimidines obtained were partially purified by column chromatography but owing to their high reactivity towards air analytically pure samples could not be obtained.[3] Their structures were established spectroscopically (see Table) and by their conversion with potassium permanganate into the corresponding 4-substituted pyrimidines (6).[2]

^{1}H n.m.r. data (δ values) for the 4-heteroaryl-1,4(or 3,4)-dihydropyrimidines (3a—e) in deuteriochloroform with tetramethylsilane as internal standard

	2-H	4-H	5-H	6-H	NH	4-Heteroaryl substituent resonances
(3a)	6.90	5.35	4.76	6.07	5.44	7.25; 6.87
(3b)	6.83	5.16	4.69	6.02	6.38	7.27—6.99
(3c)	6.94	5.18	4.66	*	*	7.28; 6.40—6.05
(3d)	6.86	5.23	4.71	6.13	5.21	6.55; 6.01; 3.69
(3e)	7.03	5.18	4.60	6.13	6.91	8.50; 8.40; 7.69; 7.24

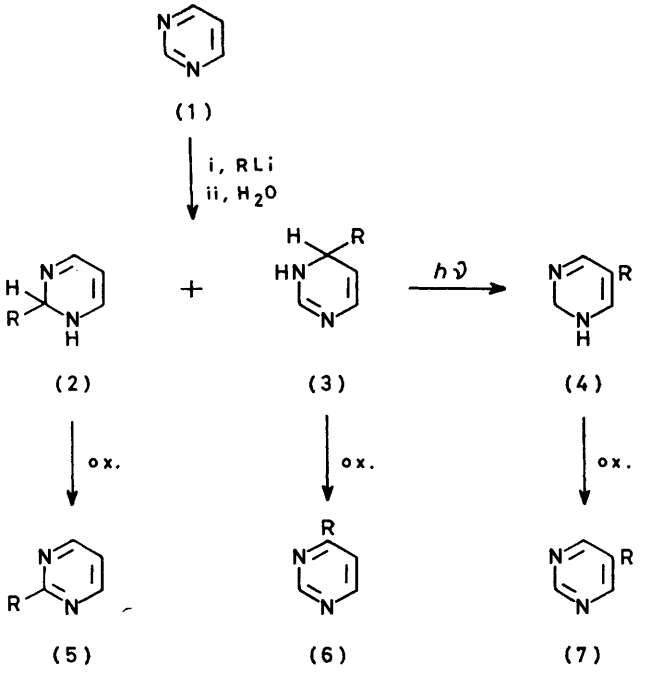
* Owing to overlap, data cannot be given.

Irradiations.—In all the 4-heteroaryl-1,4(or 3,4)-dihydropyrimidines investigated the heteroaryl substituent contains a C=C bond in the α-position and the reacting part of the molecules may be classified as a heteroaryl vinyl methane system.[4] 4-(2-Thienyl)-1,4(or 3,4)-dihydropyrimidine (3a) rearranged upon both sensitized (in acetone solution, 300 nm; acetone acts both as solvent and as sensitizer) and direct (methanol; 254 nm) irradiation. The irradiation was stopped when all starting material had disappeared. After evaporation the n.m.r. spectrum of the residue showed characteristic peaks of 5-(2-thienyl)-1,2(or 2,3-dihydropyrimidine (4a) [the CH_2 group of (4a) resonates at δ 4.55 [1a]], 4-(2-thienyl)pyrimidine (6a) [δ 8.55 (d, 6-H) and 9.04 (s, 2-H)], and 5-(2-thienyl)pyrimidine (7a) [δ 8.85 (s, 4-, 6-H) and 9.02 (s, 2-H)].

After treatment of this irradiation mixture with potassium permanganate compounds (7a) and (6a) were isolated by column chromatography in yields of 39 and 9%, respectively. In spite of the fact that deoxygenated nitrogen was bubbled through the solution prior to and during irradiation the formation of (6a) could not be avoided. It seems likely that this oxidation competes

with the rearrangement. Apparently (3a) is oxidized even faster in its excited state than in its ground state.*

Acetone-sensitized irradiation of 4-(3-thienyl)-1,4(or 3,4)-dihydropyrimidine (3b) and subsequent treatment with potassium permanganate gave 5-(3-thienyl)- (7b) and 4-(3-thienyl)-pyrimidine (6b) (6 and 28%, respectively, by g.l.c. analysis). The rate of conversion of (3b)



a; R = 2-thienyl
b; R = 3-thienyl
c; R = 2-furyl
d; R = 1-methylpyrrol-2-yl
e; R = 3-pyridyl

SCHEME 2

was slower than that of (3a), since a longer irradiation time was needed to convert (3b) completely. This may be one of the reasons why the unwanted photo-oxidation of the substrate became the main reaction course. These results, combined with those obtained from irradiation of (3a), indicate that no photo-induced rearrangement in the thienyl group occurs. This is in agreement with the observation that irradiation of 2-(2-pyridyl)thiophen leads to no rearrangement either.†

Irradiation of 4-(2-furyl)-1,4(or 3,4)-dihydropyrimidine (3c) in acetone solution and subsequent treatment with potassium permanganate gave a mixture of 5-(2-furyl)-[(7c), 20%] and 4-(2-furyl)-pyrimidine [6c), 6%]. The rate of disappearance of (3c) was comparable to that of (3a). 4-(1-Methylpyrrol-2-yl)-1,4(or 3,4)-dihydropyrimidine (3d) under the same conditions was converted much more slowly; only a 2% yield of 5-(1-methylpyrrol-2-yl)pyrimidine (7d) along with 27% of the 4-isomer (6d) was formed after subsequent treatment of the irradiation mixture with potassium permanganate (g.l.c.). Of the possible six-membered heteroaromatic substituents only the 3-pyridyl group was investigated. Upon irradiation in acetone and subsequent treatment with potassium permanganate 4-(3-pyridyl)-1,4(or 3,4)-dihydropyrimidine (3e) gave the corresponding 5-pyridylpyrimidine [(7e), 26%] along with the 4-(3-pyridyl) isomer [(6e), 2%].

These results show that pyrimidines containing the heteroaryl groups 2- or 3-thienyl, 2-furyl, 1-methylpyrrol-2-yl, and 3-pyridyl at position 5 can be obtained from pyrimidine by a procedure involving heteroarylation at position 4 and subsequent photo-rearrangement. For (7a) and (7c) this method is as useful as that recently reported [5] in which irradiation of 5-iodopyrimidine in the presence of a large excess of the appropriate heteroaromatic substance gave 5-heteroaryl substituted pyrimidines. Moreover, the 3-pyridyl compound (7e) could be prepared by our method; it is not otherwise readily available because we found that it could not be prepared by irradiation of 5-iodopyrimidine in the presence of pyridine.‡

EXPERIMENTAL

General experimental conditions were as described previously.[1a] G.l.c. analyses were performed using a Hewlett–Packard 5700A chromatograph and a glass column (length, 200 cm; o.d., 1/8 in) filled with 9.2% O.V.-275 on Chromosorb W-HP, 100—200 mesh, operating at temperatures in the range 150—230 °C. 2-Thienyl-,[2] 2-furyl-,[2] and 1-methylpyrrol-2-yl-lithium [6] were prepared by lithium–hydrogen exchange, and 3-thienyl-[7] and 3-pyridyl-lithium [2] by lithium–bromine exchange reactions with a solution of n-butyl-lithium (1.6M) in hexane as reported or by a slightly modified procedure.

Preparation of the 4-Heteroaryl-1,4(or 3,4)-dihydropyrimidines.—(i) *4-(2-Thienyl)-1,4(or 3,4)-dihydropyrimidine* (3a). Thiophen (2.10 g, 25 mmol) in ether (25 ml) was added to a solution of butyl-lithium (1.6M; 15 ml) in hexane at 0 °C. The resulting mixture was stirred for 4 h at room temperature and then cooled to 0 °C. A solution of pyrimidine (1.44 g, 18 mmol) in ether (20 ml) was added and the resulting mixture was poured into conc. hydrochloric acid (20 ml)–crushed ice (20 g). The organic layer was separated off and extracted with cold 6M hydrochloric acid (20 ml). The combined acidic layers were made

* Experiments were also carried out with samples that had been repeatedly (×3) cooled (77 K), evacuated (0.1 mmHg), and brought to atmospheric pressure and room temperature under nitrogen, but with similar results. Disproportionation of the dihydropyrimidine may perhaps take place into aromatic and further reduced species. In fact the ^1H n.m.r. spectrum of the irradiation product shows several unidentified peaks at $\delta < 2.5$. No products were isolated, however. On the other hand a very rapid photo-oxidation, as reported for various dihydroheteroaromatic compounds (T. Matsuura and I. Saito in 'Photochemistry of Heterocyclic Compounds,' ed. O. Buchard, Wiley–Interscience, New York, 1976, pp. 511—512; J. A. Barltrop and J. D. Coyle, 'Excited States in Organic Chemistry,' Wiley–Interscience, New York, 1976, pp. 308—311), by traces of oxygen or by acetone cannot be excluded.

† Several other 2-substituted thiophens did rearrange upon irradiation into 3-substituted thiophens *via* a *singlet* reaction in ether solution (H. Wijnberg, *Accounts Chem. Res.*, 1971, **4**, 65). Therefore (6a) was irradiated in ether with 254 nm light for several hours. G.l.c.–t.l.c. analysis with authentic 4-(3-thienyl)-pyrimidine as reference established that (6b) was not present in the irradiation mixture.

‡ 5-Iodopyrimidine was irradiated in pyridine and acetonitrile under conditions as described in ref. 5. G.l.c. analysis with authentic 5-(3-pyridyl)pyrimidine as reference showed that (7e) was absent.

alkaline with aqueous sodium hydroxide (at 0 °C) and thereupon extracted (×3) with chloroform. The combined organic layers were dried ($MgSO_4$), filtered, and evaporated *in vacuo*. The residue was chromatographed on a silica gel column with light petroleum (b.p. 40—60 °C)–acetone–diethylamine (10 : 10 : 1) as eluant. As the dihydropyrimidine started to leave the column the eluant was gradually replaced by a mixture of 5% diethylamine in acetone. The dihydropyrimidine (3a) was obtained as a brown oil (1.92 g; 65% yield); $\nu_{max.}$ ($CHCl_3$) 3 460, 3 435, 3 180, 1 683, 1 640, 1 635, and 1 588 cm^{-1}; $\lambda_{max.}$ (log ε) (EtOH) 240 (3.97) and 281 nm (3.36). For n.m.r. data see Table. Oxidation as reported [2] gave 4-(2-thienyl)pyrimidine (7a), m.p. 67 °C (lit.,[2] 66—67 °C).

(ii) 4-(3-*Thienyl*)-1,4(*or* 3,4)-*dihydropyrimidine* (3b). To a stirred solution of 3-thienyl-lithium (17.5 mmol) in ether–hexane at −40 °C a solution of pyrimidine (1.00 g, 12.5 mmol) in ether (15 ml) was added. The mixture was then allowed to reach room temperature and worked up as under (8). Compound (3b) was obtained as a yellow oil (1.38 g, 67% yield); $\nu_{max.}$ ($CHCl_3$) 3 430, 3 420, 3 190, 1 682, 1 648, and 1 585 cm^{-1}; $\lambda_{max.}$ (log ε) (EtOH) 240 (3.70) and 285 nm (3.11). For n.m.r. data see Table. Oxidation with potassium permanganate in acetone gave 4-(3-thienyl)-pyrimidine (6b), m.p. 88—89.5 °C (lit.,[8] 88.3—89.7 °C).

(iii) 4-(2-*Furyl*)-1,4(*or* 3,4)-*dihydropyrimidine* (3c). Furan (1.70 g, 25 mmol) in THF (10 ml) was added to a solution of butyl-lithium (1.6M; 15 ml) in hexane at 0 °C. The resulting mixture was stirred for 1 h at room temperature and then cooled to 0 °C. At 0 °C, a solution of pyrimidine (0.80 g, 10 mmol) in THF (10 ml) was added and the mixture was then poured into methanol (20 ml)–crushed ice (20 g). After separation the aqueous layer was extracted (×3) with chloroform. The combined organic layers were dried ($MgSO_4$), filtered, and evaporated *in vacuo*.

Column chromatography of the residue as described under (i) gave compound (3c) as a brown oil (1.00 g, 68% yield); $\nu_{max.}$ ($CHCl_3$) 3 465, 3 445, 3 180, 1 680(sh), 1 630, 1 620, and 1 575 cm^{-1}; $\lambda_{max.}$ (log ε) (EtOH) 281 nm (3.18). For n.m.r. data see Table. Oxidation as reported [2] gave 4-(2-furyl)pyrimidine (6c), m.p. 65—66 °C (lit.,[2] 65 °C).

(iv) 4-(1-*Methylpyrrol*-2-*yl*)-1,4(*or* 3,4)-*dihydropyrimidine* (3d). A mixture of 1-methylpyrrole (0.81 g, 10 mmol) and tetramethylethylenediamine (1.23 g) in hexane (20 ml) was added to a solution of butyl-lithium (1.6M; 7 ml) in hexane at ambient temperature. The mixture was heated under reflux for 1 h and then cooled to 0 °C. At 0 °C pyrimidine (0.60 g, 7.5 mmol) was added, and the mixture was stirred for 1 h at room temperature and worked up as described under (iii) to give compound (3d) as a brown oil (0.48 g, 40% yield); $\nu_{max.}$ ($CHCl_3$) 3 475, 3 450, 3 200, 1 685(sh), 1 680, 1 635(sh), 1 630, and 1 580 cm^{-1}; $\lambda_{max.}$ (log ε) (EtOH) 249 (3.53) and 286 nm (sh) (3.23). For n.m.r. data, see Table. Oxidation with potassium permanganate in acetone gave 4-(1-methylpyrrol-2-yl)pyrimidine (6d), m.p. 74 °C (lit.,[9] 74—75 °C).

(v) 4-(3-*Pyridyl*)-1,4(*or* 3,4)-*dihydropyrimidine* (3e). To a stirred solution of 3-pyridyl-lithium (23 mmol) in ether–hexane at −70 °C a solution of pyrimidine (1.00 g, 12.5 mmol) in ether (15 ml) was added. The mixture was stirred for 15 min and hydrolysed at this temperature with methanol–water (1 : 1). The resulting mixture was allowed to reach room temperature and the organic layer was separated off. The aqueous layer was extracted (×3) with chloroform and the combined chloroform layers were dried ($MgSO_4$), filtered, and evaporated *in vacuo*. The residue was chromatographed on a silica gel column with 5% diethylamine in acetone as eluant. As the dihydropyrimidine started to leave the column the eluant was gradually replaced by 5% diethylamine in methanol. Compound (3e) was obtained as a brown oil (0.59 g, 30% yield); $\nu_{max.}$ ($CHCl_3$) 3 475, 3 455(sh), 3 220, 1 684, 1 630, 1 595, and 1 583 cm^{-1}; $\lambda_{max.}$ (log ε) (EtOH) 260 (3.37) and 294 nm (sh) (3.02). For n.m.r. data see Table. Oxidation as reported [2] gave 4-(3-pyridyl)pyrimidine (6e), m.p. 87—88 °C (lit.,[2] 89 °C. The fractions obtained by column chromatography which did not contain (3e), after oxidation and subsequent column chromatography (silica gel; chloroform–ethyl acetate, 4 : 1) gave 2-(3-pyridyl)pyrimidine (5e) (0.10 g) m.p. 48—49 °C (after isolation by g.l.c.); δ($CDCl_3$) 9.58 (1 H, s), 8.74 (4 H, m), and 7.30 (2 H, m); picrate, m.p. 190—192 °C (from EtOH) (Found: C, 46.6; H, 2.5. $C_{15}H_{10}N_6O_7$ requires C, 46.6; H, 2.6%).

Irradiations.—Irradiations were performed in a Rayonet RPR-208 preparative photochemical reaction vessel equipped with eight RUL 300 nm lamps at ambient temperature. Deoxygenated nitrogen [by activated BTS Katalysator (B.A.S.F.)] was bubbled through solutions of the dihdropyrimidines in 500 ml of acetone in a quartz vessel for 1 h before and during irradiation. The solutions of the dihydropyrimidine were irradiated until all starting material had disappeared, as shown by liquid–liquid chromatography using a Chromatronix model 3500 apparatus with a stainless steel column (10 cm × 4.6 mm) filled with Partisil 5 μm silica gel, with 1% acetonitrile in hexane–dioxan–n-butylamine (14 : 5 : 1) as eluant and with u.v. detection at 254 nm. The course of the reaction of (3e) was monitored by n.m.r. spectroscopy. After irradiation solvents were evaporated off *in vacuo* and reaction products worked up as described later. Oxidations were carried out with potassium permanganate in acetone,[1a] the resulting mixtures were filtered, and solvents evaporated off *in vacuo*. The 4-substituted pyrimidines obtained after irradiation were identified by comparison of spectral data with those of reference samples.

(i) 4-(2-Thienyl)-1,4(or 3,4)-dihydropyrimidine (3a), (500 mg) was irradiated for 75 min. After oxidation the residue was chromatographed (×2) on a silica gel column with hexane–ethyl acetate (2 : 1) as eluant, yielding 5-(2-thienyl)pyrimidine (7a) (194 mg, 39%), m.p. 76 °C (lit.,[5] 75 °C) and 4-(2-thienyl)pyrimidine (6a) (46 mg, 9%).

(ii) 4-(3-Thienyl)-1,4(or 3,4)-dihydropyrimidine (3b) (500 mg) was irradiated for 6.5 h. After oxidation the residue was chromatographed on a silica gel column with hexane–ethyl acetate (2 : 1) as eluant, yielding 170 mg of an 18 : 82 mixture of 5-(3-thienyl)- (7b) and 4-(3-thienyl)-pyrimidine (6b) as determined by g.l.c. analysis. These compounds could not be separated by column chromatography or t.l.c. Compound (7b) was isolated by g.l.c., m.p. 59—60.5 °C (lit.,[5] 61 °C).

(iii) 4-(2-Furyl)-1,4(or 3,4)-dihydropyrimidine (3c) (500 mg) was irradiated for 105 min. After oxidation the residue was chromatographed on a silica gel column with chloroform–ethyl acetate (4 : 1) as eluant, yielding 5-(2-furyl)pyrimidine (7c) (100 mg, 20%), m.p. 55—57 °C (lit.,[5] 57 °C) and 4-(2-furyl)pyrimidine (6c (28 mg, 6%).

(iv) 4-(1-Methylpyrrol-2-yl)-1,4(or 3,4)-dihydropyrimidine (3d) (250 mg) was irradiated for 3.5 h. After oxidation the residue was chromatographed (×2) on a silica gel column, with chloroform–ethyl acetate (1 : 1) as eluant,

yielding 4-(1-methylpyrrol-2-yl)pyrimidine (6d) (64 mg) and a 1 : 1 mixture (11 mg) of (6d) and 5-(1-methylpyrrol-2-yl)pyrimidine (7d). The identity of (7d) was confirmed by comparison (n.m.r., t.l.c., g.l.c.) with an authentic sample, prepared as already described.[5]

(v) 4-(3-Pyridyl)-1,4(or 3,4)-dihydropyrimidine (3e) (250 mg) was irradiated for 2 h. After oxidation the residue was chromatographed on a silica gel column with acetone as eluant, yielding 5-(3-*pyridyl*)*pyrimidine* (7e) (64 mg, 26%), m.p. 107—108 °C (from light petroleum, b.p. 60—80 °C) (Found: C, 68.9; H, 4.2. $C_9H_7N_3$ requires C, 68.8. H, 4.5%); δ($CDCl_3$) 9.22 (1 H, s), 8.95 (2 H, s), 8.84 (1 H, d, *J* 2.3 Hz), 8.70 (1 H, dd, *J* 2.0 and 4.7 Hz), 7.93 (1 H, m), and 7.44 (1 H, dd, *J* 4.7 and 8.0 Hz). 4-(3-Pyridyl)pyrimidine (6e) (6 mg, 2%) was also obtained.

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