A NEW HETEROCYCLIC REARRANGEMENT: CONVERSION OF 1,2-DIHYDROPYRIMIDINES INTO PYRROLES

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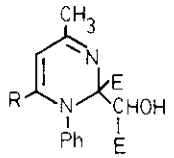
Abstract- 2-[Hydroxy(methoxycarbonyl)methyl]-2-(methoxycarbonyl)-1-phenyl-1,2-dihydropyrimidines react with acetic anhydride to give 2-methoxycarbonyl pyrroles. A reaction intermediate has been isolated and a mechanism is proposed for the reaction process.

1,2-Dihydropyrimidines 1[1] react with refluxing acetic anhydride to give a mixture of acetanilide 2 and pyrroles 3 and 4. When the reaction of 1a with acetic anhydride is carried out in toluene as solvent, together with 3a and traces of 4a, a new compound 5a is isolated. In the latter conditions, no acetanilide is detected.



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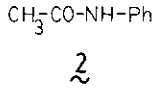

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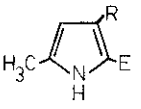

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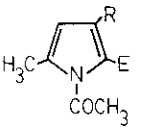

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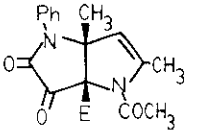
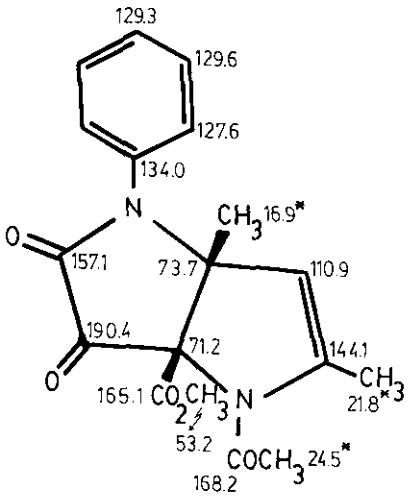


5a

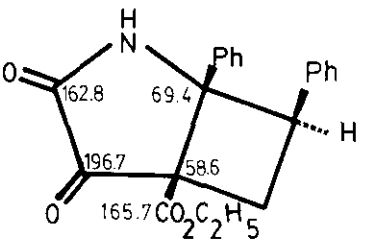
a R=CH_3 b R=H E=CO_2CH_3

Pyrroles 3 and 4 have been identified by their ^{1}H- and ^{13}C-nmr spectra[2,3] together with their characteristic mass fragmentation[4].

The structure of compound 5a has been established on the basis of its spectroscopic data, specially its mass spectrum which shows the successive transformation into 4a and 3a, and its ^{13}C-nmr spectrum assigned by comparison with the known compounds 6[5] and 7[6]. Signals at 71.2 and 144.1 ppm are broadened by slow rotation of the N-acetyl group. The chemical shifts of the methyl carbon atoms can been interchanged.



5a



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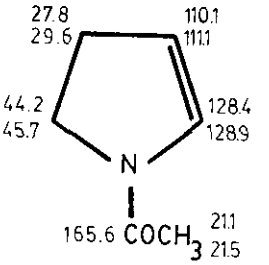

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We propose the following mechanism for the rearrangement of 1 into 3,4 and 5 (see Scheme 1).

When 1a is dissolved in acetic anhydride, at room temperature, it is immediately O-acetylated, as it has been experimentaly verified. This acetate could react through its open chain tautomer by two alternative pathways.

Path a: Acetylation on the central nitrogen atom followed by double cyclization gives compound 5.

Path b: Acetylation on the N-phenyl nitrogen atom and cyclization forms pyrrole 3 with loss of acetanilide.

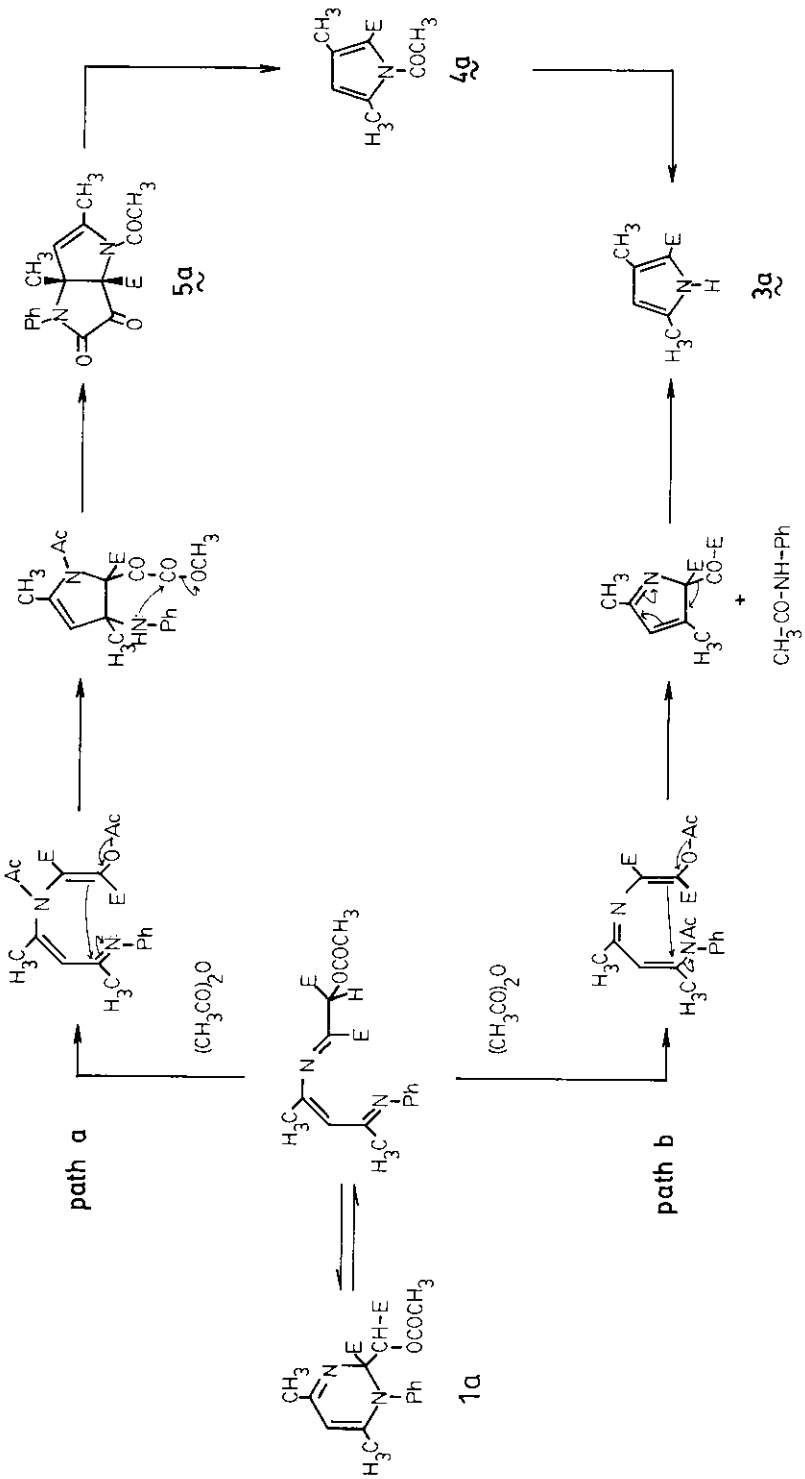
We have experimentally verified that compound 5a affords pyrroles 3a and 4a in refluxing acetic anhydride. Moreover, pyrrole 3a is not acetylated to 4a in the reaction conditions; therefore, compound 4 must be formed directly from 1, via path a), and not by acetylation of 3.

From the nature of the reaction products it seems that both pathways, a) and b), are possible in refluxing acetic anhydride, but in refluxing toluene as solvent only path a) occurs, as the absence of acetanilide suggests.

This is, to our knoweledge, the first example of a ring contraction of 1,2-dihydropyrimidines to pyrroles, although such an intermediate has been proposed in the electrochemical ring contraction of pyrimidines into pyrroles[7].

EXPERIMENTAL

Melting points were determined on a Büchi 510 D apparatus and are uncorrected.



SCHEME 1

Ir spectra were recorded on a Perkin-Elmer 781 spectrophotometer, ^{1}H-nmr spectra on a Varian T-60A spectrometer, ^{13}C-nmr spectra on a Varian FT-80A spectrometer and mass spectra on a Varian MAT-711 spectrometer.

Reaction of 1,2-dihydropyrimidines 1 in acetic anhydride

Compound 1 (6 mmol) was dissolved in 2.3 ml of dry acetic anhydride and refluxed for 2 h.The cold mixture was poured into 150 ml of ice-water, extracted with chloroform (3 x 20 ml) and the organic layer was dried over anhydrous magnesium sulfate. The solvent was removed in vacuum and the residue was chromatographed on silica gel and eluted with petroleum ether/ethyl acetate (9:1) to give pyrroles 3 and 4 and acetanilide 2.

Compound 1a gave:

16% of 3,5-dimethyl-2-(methoxycarbonyl)pyrrole 3a, mp 97-98°C (sublimed at 40°C/10^{-3} mbar); ms: m/z (%) 153 (M^+, 100), 122 (66), 121 (75), 120 (32), 94 (16), 93 (17), 67 (16), 66 (27); ir: ν_{max} (KBr) 3290 (NH), 1675 (C=O), cm^{-1}; ^{1}H-nmr: $\delta(DCCl_3)$ 2.23 (s, 3H, CH_3-3), 2.30 (s, 3H, CH_3-5), 3.80 (s, 3H, OCH_3), 5.77 (bs, 1H, H-4), 8.3-9.1 (bs, 1H, NH) ppm; ^{13}C-nmr $\delta(DCCl_3)$ 13.0 (CH_3-3 and CH_3-5), 50.4 (OCH_3). 111.1 C-4), 117.3 (C-2), 128.8 (C-3), 133.0 (C-5), 162.5 ($\underline{C}O_2CH_3$) ppm; Anal. Calcd for $C_8H_{11}NO_2$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.50; H, 7.40; N, 8.90.

4% of 1-acetyl-3,5-dimethyl-2-(methoxycarbonyl)pyrrole 4a, mp 47-48°C (sublimed at 30°C/10^{-3} mbar); ms: m/z (%) 195 (M^+, 12), 153 (100), 122 (40), 121 (66), 94 (6), 93 (10); ir: ν_{max}(KBr) 1720 (CON), 1685 (COO) cm^{-1}; ^{1}H-nmr: $\delta(DCCl_3)$ 2.27 (s, 6H, CH_3CO and CH_3-3), 2.43 (s, 3H, CH_3-5), 3.77 (s, 3H, OCH_3), 5.72 (s, 1H, H-4) ppm; ^{13}C-nmr: $\delta(DCCl_3)$ 13.3 (CH_3-3), 14.0 (CH_3-5), 28.3 ($\underline{C}H_3CO$), 51.6 (OCH_3), 113.7 (C-4), 120.1 (C-2), 133.8 (C-3), 136.6 (C-5), 162.0 ($\underline{C}O_2CH_3$), 173.6 (CO-N) ppm; Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.17. Found: C, 60.10; H, 6.70; N, 7.10.

53% of acetanilide 2.

Compound 1b gave:

5% of 5-methyl-2-(methoxycarbonyl)pyrrole 3b, mp 75-76°C (sublimed at 40°C/10^{-3} mbar); ms: m/z (%) 139 (M^+, 100), 108 (92), 107 (53), 80 (21), 79 (30), 53 (21), 52 (19); ir: ν_{max}(KBr) 3310 (NH), 1675 (C=O) cm^{-1}; ^{1}H-nmr: $\delta(DCCl_3)$ 2.33 (s, 3H, CH_3-5), 3.83 (s, 3H, OCH_3), 5,93 (m, J=3.6, 2.6 and 0.8 Hz, 1H, H-4), 6.80 (t, J= 2.6 Hz, 1H, H-3), 8.8-10.5 (bs, 1H, NH); ^{13}C-nmr: $\delta(DCCl_3)$ 13.1 (CH_3-5), 51.2 (OCH_3), 109.0 (C-4), 116.4 (C-3), 121.1 (C-2), 134.2 (C-5), 162.0 ($\underline{C}O_2CH_3$) ppm; Anal. Calcd for $C_7H_9NO_2$: C, 60.42; H, 6.52; N, 10.06. Found: C, 60.20; H, 6.60; N, 9.90.

13% of 1-acetyl-5-methyl-2-(methoxycarbonyl)pyrrole 4b, mp 57-58°C (sublimed at

30°C/10^{-3} mbar); ms: m/z (%) 181 (M^+, 16), 139 (100), 108 (67), 107 (53), 80 (10), 79 (16), 53 (14), 52 (14); ir: ν_{max}(KBr) 1730 (CON), 1690 (COO) cm^{-1}; ^{1}H-nmr: $\delta(DCCl_3)$ 2.30 (s, 3H, CH_3CO), 2.50 (s, 3h, CH_3-5), 3.80 (s, 3H, OCH_3), 5,90 (m, J= 3.6 and 0.8 Hz, 1H, H-4), 6.83 (d, J=3.6 Hz, 1H, H-3) ppm; ^{13}C-nmr: $\delta(DCCl_3)$ 13.9 (CH_3-5), 28.1 ($\underline{C}H_3CO$), 51.6 (OCH_3), 110.3 (C-4), 121.0 (C-3), 123.1 (C-2), 137.6 (C-5), 161.1 ($\underline{C}O_2CH_3$), 173.6 (CO-N) ppm; Anal. Calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.50; H, 6.10; N, 7.50.

17% of acetanilide 2.

Reaction of 1,2-dihydropyrimidine 1a with acetic anhydride in toluene

A solution of 3 mmol of 1a and 9 mmol of dry acetic anhydride in 30 ml of dry toluene was refluxed for 2.5 h. The excess of acetic anhydride and toluene were removed in vacuum and the residue was recrystallized from toluene to give 33% of 5-acetyl-6,8-dimethyl-4-(methoxycarbonyl)-2,3-dioxo-1-phenyl-2,3,4,8-tetrahydropyrrolo 3,2-b pyrrole 5a, mp 202-203°C; ms: m/z (%) 342 (M^+, 18), 300 (15), 195 (28), 153 (100), 122 (19), 121 (31), 120 (8), 94 (10), 93 (11), 67 (11), 66 (13); ir: ν_{max}(KBr) 1770 (COO), 1715 (CON), 1660, 1640 cm^{-1}; ^{1}H-nmr: $\delta(DCCl_3)$ 1.36 (s, 3H, CH_3-8), 2.30 (d, J=1.2 Hz, 3H, CH_3-6), 2.33 (s, 3H, CH_3CO), 3.73 (s, 3H, OCH_3), 5.00 (q, J=1.2 Hz, 1H, H-7), 6.7-7.6 (m, 5H, C_6H_5) ppm; Anal. Calcd for $C_{18}H_{18}N_2O_5$: C,63.15; H, 5.30; N, 8.18. Found: C, 63.20; H, 5.29; N, 8.30.

The mother liquors were evaporated and the residue, identified by tlc as 3a with traces of 4a, was chromatographed on silica gel and eluted with petroleum ether/ethyl acetate (9:1) to give 24% of 3a.

Reaction of 1,2-dihydropyrimidine 1a with acetic anhydride at room temperature

Compound 1a (0.6 mmol) was stirred with 2.5 mmol of dry acetic anhydride until disolution. The mixture was poured into 25 ml of ice-water, extracted with chloroform (3 x 5 ml) and dried over magnesium sulfate. The solvent was removed in vacuum and the residual yellow oil was identified by ^{1}H-nmr as the O-acetate of 1a (mixture of two diastereoisomers) $\delta(DCCl_3)$ 1.60 and 1.63 (s, 3H, CH_3-6), 1.90 and 2.15 (s, 3H, CH_3CO), 2.08 and 2.15 (s, 3H, CH_3-4), 3.50, 3.65, 3.70 and 3.73 (s, 3H, OCH_3), 5.08 and 5.25 (s, 1H, CHOAc), 5.67 and 5.75 (bs, 1H, H-5), 7.35 (m, 5H, C_6H_5) ppm.

Reaction of 5a with acetic anhydride

A solution of 0.12 mmol of 5a in 0.98 mmol of dry acetic anhydride was refluxed for 2 h. The cold mixture was poured into 10 ml of ice-water, extracted with chloroform (3 x 5 ml) and dried over sodium sulfate. The solvent was removed in vacuum and the crude product was identified by tlc as 3a with traces of 4a.

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