BASE-CATALYSED CONDENSATION OF 2,5-DIMETHYL-1-PHENYLPYRROLE-3,4-DICARBALDEHYDE WITH β-DIKETONES

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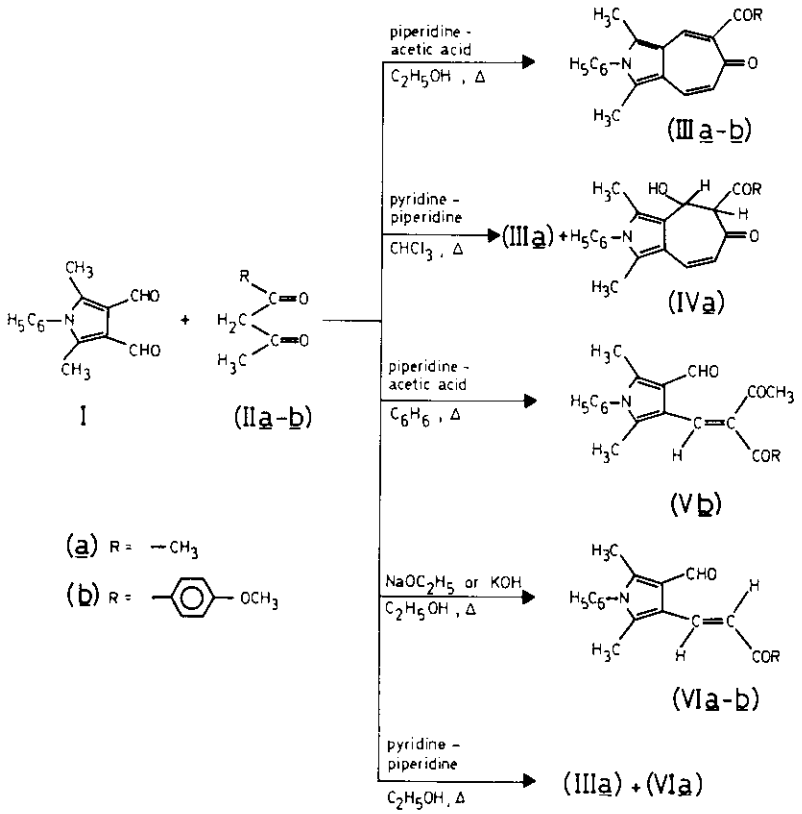
Abstract - The base-catalysed condensation of 2,5-dimethyl-1-phenylpyrrole-3,4-dicarbaldehyde with 2,4-pentanedione and 1-(p-methoxyphenyl)-1,3-butanedione has been investigated under different reaction conditions (e.g. solvent, catalyst, temperature, time).

Base-catalysed condensations of pyrrole-o-dicarbaldehydes with ketones are well documented[1-7], but there are no data on the condensation with β-diketones except the paper of Davey and Gottfried[8] describing the condensation of o-phthalaldehyde with 2,4-pentanedione. In this paper we would like to describe in full the experimental details of the base-catalysed condensation of 2,5-dimethyl-1-phenylpyrrole-3,4-dicarbaldehyde with β-diketones of the type $R-CO-CH_2-CO-CH_3$ (where $R=CH_3$ and $C_6H_5OCH_3$), which leads, depending on the reaction conditions applied, to the formation of troponoid systems or α,β-unsaturated carbonyl compounds.

2,5-Dimethyl-1-phenylpyrrole-3,4-dicarbaldehyde (I) reacts over a period of 6-12 h with β-diketones (IIa - b) in the presence of piperidine-acetic acid in boiling ethanol, giving 5-substituted 6H-cyclohepta[c]pyrrol-6-ones (IIIa - b). The compounds were purified by using tlc on silica gel and chloroform-acetone (9:1 v/v) as eluent. The yields were 34% and 25%, respectively.

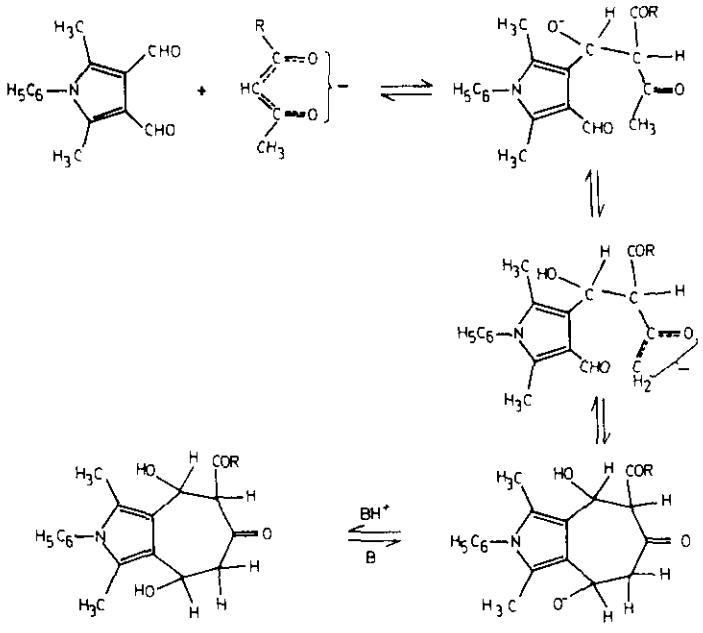
By condensation of (I) with (IIa) in boiling chloroform over a period of 4 h, using a mixture of pyridine-piperidine as catalyst, a mixture of 5-substituted 6H-cyclohepta[c]pyrrol-6-ones (IIIa) and an intermediate aldol (IVa) was obtained. Purification of the product by tlc and subsequent recrystallization from benzene-petroleum ether (1:1 v/v) gave compound (IIIa) in the yield of 15% and compound (IVa) in the yield of 25%. When (I) reacted with (IIb) in boiling benzene using piperidine-acetic acid as catalyst, water being removed by a Dean-Stark attachment, another type of transformations was encountered. It was shown that the

product did not contain a seven-membered ring, but was actually an α,β-unsaturated ketone of the type (V<u>b</u>). The condensation of (I) with (II<u>a</u> - <u>b</u>) in boiling ethanol in the presence of sodium ethoxide or potassium hydroxide as catalyst over a period of 2 h gave α,β-unsaturated ketones (VI<u>a</u> - <u>b</u>).



It seems that the basic cleveage of β-diketones was effected by a mechanism of reversal of the Claisen condensation. This was confirmed by condensation of equimolar quantities of (I) and <u>p</u>-methoxyacetophenone under the same reaction conditions. When (I) reacted with (II<u>a</u>) in boiling ethanol using a mixture of pyridine-piperidine as catalyst, a mixture of 5-substituted 6<u>H</u>-cyclohepta[<u>c</u>]pyrrol-6-one (III<u>a</u>) and α,β-unsaturated ketone (VI<u>a</u>) was obtained. The compounds were purified by using <u>tlc</u> on silica gel and chloroform-acetone (9:1 v/v) as eluent. The yields were 29% and 18%, respectively. The compound (VI<u>b</u>) was also characterized through the formation of its oxime (VII<u>b</u>).

The mechanism of the seven-membered ring formation may be plausibly represented by the following scheme:



The experimental evidence, which supports this mechanism is the isolated intermediate aldol (IV)[8]. The reaction proceeds by the formation of a resonance-stabilized enolate ion which attacks the carbonyl carbon of dialdehyde giving an alkoxide ion. In the next step the proton transfer leads predominantly to an intermediate aldol product which undergoes intramolecular ring closure and subsequent base-catalysed dehydration resulting the compounds (IV) and (III). Two resonable mechanisms would seem possible to explain the formation of α,β-unsaturated carbonyl compound (V), although experimental evidence is not available to support them. One could be a base-catalysed aldol condensation giving rise to a β-hydroxycarbonyl compound which readilly undergoes acid-catalysed dehydration, and the other could be explained as an overall acid-catalysed process.

EXPERIMENTAL

Melting points were determined on a Büchi apparatus and are not corrected. The ir spectra were recorded on a Perkin-Elmer Model 227 and Model 377 spectrophotometers in KBr discs. The ^{1}H nmr spectra were recorded on a Varian T-60 or Joel JNM-FX 100 FT spectrometer with tetramethylsilane as the internal reference. Preparative thin-layer chromatography (tlc) was carried out on tlc plates (silica gel 60 F_{254} pre-coated, 2 mm thickness) with chloroform-acetone (9:1 v/v) as eluent and the plates were scaned under ultraviolet light, λ=254 and 366 nm. All solvents were evaporated on a Devarot evaporator at a water-aspirator pressure using a water bath set at 35-60°C.

5-Acetyl-1,3-dimethyl-2-phenyl-6H-cyclohepta[c]pyrrol-6-one (IIIa)

To a boiling solution of 2,5-dimethyl-1-phenylpyrrole-3,4-dicarbaldehyde (I) (1.14 g, 0.005 mol) and 2,4-pentanedione (IIa) (1.00 g, 0.005 mol) in absolute ethanol (25 ml), piperidine (10 drops) and acetic acid (6 drops) were added. The reaction mixture was heated under reflux for 6 h and allowed to stand at room temperature for 7 days. Removal of the solvent left the crude product, which was purified by tlc. Recrystallization from benzene-petroleum ether (1:1 v/v) gave the analitically pure pale-yellow crystals of (IIIa) (0.50 g; 34%), mp 165-166°C; ir (KBr) 1685, 1615, 1595, 1570 (C=O, C=C) cm^{-1}; nmr ($CDCl_3$) δ 2.20 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 6.43 (d, J=12.3 Hz, 1H, C_7-H), 7.16-7.60 (m, 6H, aromatic + C_8-H), 8.02 (s, 1H, C_4-H).

5-p-Anisoyl-1,3-dimethyl-2-phenyl-6H-cyclohepta[c]pyrrol-6-one (IIIb)

To a boiling solution of (I) (1.14 g, 0.005 mol) and 1-(p-methoxyphenyl)-1,3-butanedione (IIb) (0.96 g, 0.005 mol) in absolute ethanol (40 ml), piperidine (10 drops) and acetic acid (6 drops) were added. The reaction mixture was heated under reflux for 12 h and allowed to stand at room temperature for 7 days. After evaporation of the mixture to dryness, the oily semisolid residual was triturated with ether and the unchanged starting material filtered off. Removal of the solvent left the crude residue, which was purified by tlc. Recrystallization from benzene-petroleum ether (1:1 v/v) gave (IIIb) as yellow crystals (0.24 g; 25%) mp 200-202°C; ir (KBr) 1650, 1595, 1580 (C=O, C=C) cm^{-1}; nmr ($CDCl_3$) δ 2.25 (s, 6H, CH_3), 3.80 (s, 3H, OCH_3), 6.37 (d, J=13.8 Hz, 1H, C_7-H), 6.65-8.00 (m, 11H,

aromatic, C_4-H, C_8-H).

5-Acetyl-4,5-dihydro-4-hydroxy-1,3-dimethyl-2-phenyl-6H-cyclohepta[c]pyrrol-6-one (IVa)

Compounds (I) (1.14 g, 0.005 mol) and (IIa) (0.50 g, 0.005 mol) were dissolved in chloroform (10 ml), and to this were added piperidine (4 drops), and pyridine (4 drops), and the reaction mixture was heated under reflux for 4 h. After being left at room temperature for one day, the mixture was evaporated to dryness and the oily residue was triturated with ether affording a crude product (1.00 g). Purification by tlc and recrystalization from benzene-petroleum ether (1:1 v/v) gave 0.22 g (15%) of compound (IIIa), mp 165-167°C and 0.38 g (25%) of compound (IVa) as yellow crystals, mp 143-144°C; ir (KBr) 3410 (O-H), 1660, 1648 (C=O, C=C) cm^{-1}; nmr ($CDCl_3$) δ 1.21 (d, J=4.5 Hz, 1H, C_4-H), 1.70 (s, 3H, CH_3), 1.77 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 2.73 (d, J=4.5 Hz, 1H, C_5-H), 4.57 (broad, 1H, OH), 5.89 (d, J=12.3 Hz, 1H, HC=C), 6.64-7.13 (m, 5H, aromatic), 7.58 (d, J=12.3 Hz, 1H, C=CH).

(E)-4-(2-p-Anisoyl-3-oxo-1-butenyl)-2,5-dimethyl-1-phenylpyrrole-3-carbaldehyde (Vb)

Compounds (I) (1.14 g, 0.005 mol) and (IIb) (0.96 g, 0.005 mol) were dissolved by heating in benzene (40 ml), and to this were added piperidine (1 drop) and acetic acid (4 drops). The reaction mixture was refluxed for 4 h, water being removed by a Dean-Stark attachment. After being left at room temperature for 7 days, the solution was evaporated to dryness and the crude residue triturated with ether. The unchanged starting material was filtered off, the filtrate evaporated, and the residue purified by tlc. Recrystallization from benzene-petroleum ether afforded 0.69 g (62%) of the compound (Vb) as pale-yellow crystals, mp 139-140°C; ir (KBr) 1660-1640 (C=O, C=C) cm^{-1}; nmr ($CDCl_3$) δ 1.70 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 6.65-7.86 (m, 9H, aromatic), 8.23 (s, 1H, ethylenic), 9.92 (s, 1H, CHO).

(E)-4-(3-Oxo-1-butenyl)-2,5-dimethyl-1-phenylpyrrole-3-caraldehyde (VIa)

Method A:

A hot solution of (I) (0.23 g, 0.001 mol) and (IIa) (0.10 g, 0.001 mol) in absolute ethanol (5 ml) was added dropwise to a stirred solution of sodium ethoxide in ethanol (0.09 g Na/10 ml ethanol). The reaction mixture was stirred and refluxed

for 4 h and allowed to stand at room temperature for 7 days. The solution was chilled in ice bath and acidified with 5% hydrochloric acid to give yellow precipitate. Purification by tlc and recrystallization from absolute ethanol afforded 0.20 g (73%) of compound (VIa) as yellow crystals, mp 139-142°C; ir (KBr) 1685 (C=O aldehydic), 1670, 1655 (C=O, C=C), 1285, 950 (HC=CH trans) cm^{-1}; nmr ($CDCl_3$) δ 2.24 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 6.44 (d, J=12.3 Hz, 1H, ethylenic), 7.14-7.61 (m, 5H, aromatic), 8.02 (d, J=12.3 Hz, 1H, ethylenic), 10.35 (s, 1H, CHO).

Method B:

To a boiling solution of (I) (0.45 g, 0.002 mol) and (IIa) (0.20 g, 0.002 mol) in absolute ethanol (20 ml), piperidine (2 drops) and pyridine (2 drops) were added. The reaction mixture was heated under reflux for 4 h. After being left at room temperature for one day, the unchanged starting material was filtered off and the mixture was evaporated to dryness. Purification by tlc and recrystallization from benzene-petroleum ether (1:1 v/v) gave 0.12 g (29%) of compound (IIIa), mp 165-167°C and 0.07 g (18%) of compound (VIa), mp 139-142°C.

(E)-4-(2-p-Anisoyl-1-ethenyl)-2,5-dimethyl-1-phenylpyrrole-3-carbaldehyde (VIb)

Method A:

A hot solution of (I) (0.68 g, 0.003 mol) and (IIb) (0.58 g, 0.003 mol) in absolute ethanol (20 ml) was added to a stirred solution of sodium ethoxide in ethanol (0.28 g Na/20 ml ethanol). The resulting red solution was stirred and refluxed for 2 h and allowed to stand at room temperature for 7 days. Water was added to effect precipitation, and the precipitated solid was collected and purified by tlc. Recrystallization from absolute ethanol afforded 0.46 g (43%) of compound (VIb) as yellow crystals, mp 180-182°C.

Method B:

Compound (I) (1.14 g, 0.005 mol) and (IIb) (0.98 g, 0.005 mol) were dissolved in 95% ethanol (40 ml), and 50% aqueous potassium hydroxide (2.5 ml) was added to the stirred solution dropwise. The reaction mixture was stirred and refluxed for 2 h. On cooling, the solution was acidified with 5% hydrochloric acid and chilled in ice bath to give a yellow crystalline precipitate, which was collected by filtration,

washed with water until neutral and dried. Purification by tlc and recrystallization from ethanol gave 0.87 g (48%) of compound (VIb) as yellow crystals, mp 180-182°C; ir (KBr) 1660 (C=O aldehydic), 1640, 1635 (C=O, C=C), 1290, 960 (HC=CH trans) cm^{-1}; nmr ($CDCl_3$) 2.15 (s, 3H, CH_3), 2.25 (s, 3H, CH_3) 3.80 (s, 3H, OCH_3) 6.75-8.20 (m, 11H, aromatic + ethylenic), 10.15 (s, 1H, CHO).

(E)-4-(2-p-Anisoyl-1-ethenyl)-2,5-dimethyl-1-phenylpyrrole-3-carbaldehyde Oxime (VIIb)

A solution of (VIb) (0.09 g, 0.25 mmol), hydroxylamine hydrochloride (0.034 g, 0.50 mmol) and sodium acetate (0.05 g) in ethanol (10 ml) and water (0.5 ml) was heated under reflux for 1 h. After addition of water, recrystallization of the resulting precipitate from aqueous ethanol afforded the oxime (VIIb) (0.045 g, 48%) as yellow crystals, mp 202-203°C; ir (KBr) 3500 (O-H), 1638 (C=O, C=C, C=N) cm^{-1}; nmr ($CDCl_3$) δ 2.12 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 7.04-8.39 (m, 12H, aromatic + 2 ethylenic + azomethinic).

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