

ALKYLATION REACTIONS OF THE MANNICH BASES

Part. II.—1-(N, N-Dimethylamino)-3-Keto-5-Phenylpent- Δ^4 -ene and 1-(N, N-Dimethylamino)-3-Keto-5-Phenylpentane, in Aqueous Medium

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Alkylation of indole, pyrrole, phthalimide with 1-(N,N-Dimethylamino)-3-keto-5-phenylpent- Δ^4 -ene¹ and of pyrrole, nitromethane, phthalimide, cyanoacetamide and piperazine with 1-(N,N-Dimethylamino)-3-keto-5-phenylpentane are described.

In earlier communications we described alkylation reactions of the Mannich bases, *viz.*, gramine² and Phenyl- β dimethylamino-ethyl ketone³ in water.

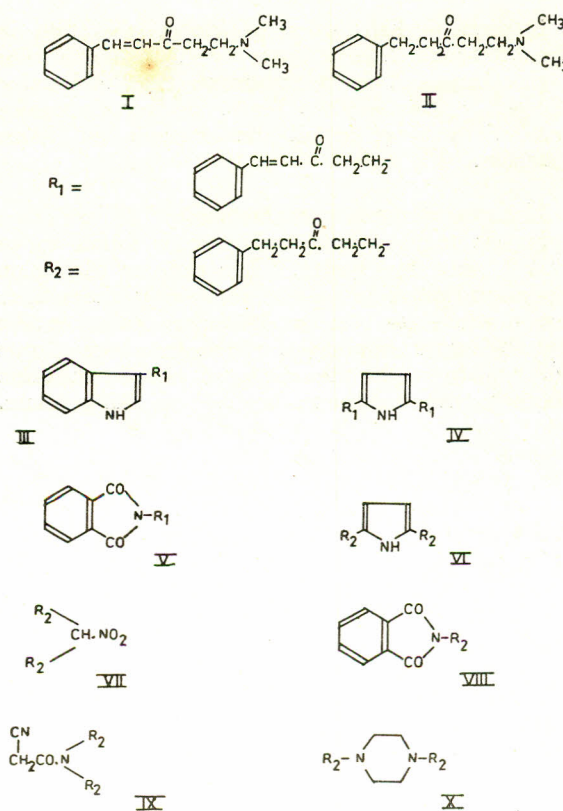
Encouraged by these findings which pointed towards the alkylation of suitable compounds with the Mannich bases as a likely general reaction we have continued our alkylation studies with a number of other Mannich bases. In the present communication we report our studies on the alkylation of indole, pyrrole and phthalimide with Mannich bases: 1-(N,N-dimethylamino)-3-keto-5-pent- Δ^4 -ene (I) and of pyrrole, nitromethane, phthalimide, cyanoacetamide and piperazine with the Mannich base, 1-(N, N-Dimethylamino)-3-keto-5-phenylpentane (II), in water.

With the hydrochloride of the unsaturated base (I) indole gets alkylated, β -(3-keto-5-phenylpent- Δ^4 -enyl)-indole (III), m.p. 127°C, being obtained in about 65.9% yield. In the case of pyrrole, dialkylation with the hydrochloride of the base (I) takes place in the α, α' positions in almost quantitative yields and the product, α, α' -di(3-keto-5-phenylpent- Δ^4 -enyl) pyrrole, m.p. 133°C, is obtained in about 98% yield. Alkylation of ammonium carbonate, nitromethane, cyanoacetamide and potassium cyanide in water and in toluene failed to give any satisfactorily characterisable products.

With phthalimide the alkylation reaction with the free base goes smoothly to give N-(3 keto-5-phenylpent- Δ^4 -enyl)-phthalimide (V).

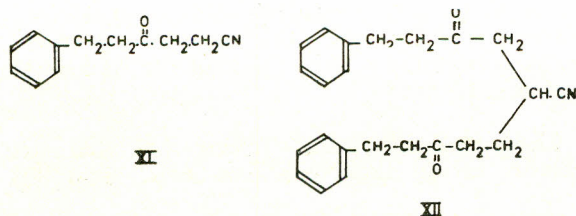
Similarly alkylation studies of the saturated base, 1-(N, N-dimethylamino)-3-keto-5-phenylpentane (II), were, however, more fruitful. Alkylation of pyrrole, nitromethane, cyanoacetamide and piperazine gave dialkylated products, *viz.*, α, α' -di(3-keto-5-phenylpentyl) pyrrole (VI), m.p. 88°C; di-(3-keto-5-phenylpentyl)-nitromethane (VII) m.p. 86°C; N, N-di-keto-5-phenyl cyanoacetamide (IX) m.p. 158°C., and N, N'-di(3-keto-5-phenylpentyl)-piperazine (X) m.p. 80°C, in

very high yields. With phthalimide the product, (N-(3-keto-5-phenylpentyl)-phthalimide (VIII), m.p. 102°C, is obtained in 72% yield.



As in the case of the unsaturated base (I), alkylation of methylcyanide and ammonium carbonate with the base (II) yielded products which could not be purified or characterised. With potassium cyanide, however, two products in minute quantities were obtained and that too only once. The product, m.p. 208°-209°C, analysed for what we believe to be 1-cyano-3-keto-5-phenylpentane. The second product which was oily analysed for $\text{C}_{23}\text{H}_{25}\text{O}_2\text{N}$ and could be 1,10-

diphenyl-3, 8-diketo-6-cyano-decane on the assumption that after the initial alkylation, the product 1 - cyano - 3 - keto - 5 - phenylpentane, again gets alkylated, the substitution now taking place supposedly at the methylene group adjoining the -CN. Several variations in the experimental conditions have so far failed to give the two products. Attempts, however, are still continuing and if successful will be reported later.



Experimental

All melting points are corrected. I.R. Spectra were recorded with a Beckmann I.R.-5.

GENERAL METHOD

The Mannich base 1-(N, N-Dimethylamino)-keto-5-phenylpent- Δ^4 -ene (I) or 1-(N,N-Dimethylamino)-3-keto-5-phenylpentane (II) and the reactant to be alkylated were suspended in water and the mixture heated on water bath or refluxed on sand bath. After completion of the reaction the product if oily was isolated with ether or ethylacetate and if solid through filtration (suction) and crystallised from appropriate solvent.

The alkylated products reported are generally moderately to easily soluble in acetone, benzene, dioxane, ethyl acetate, chloroform, ether, ethanol and methanol and insoluble in light-petroleum (65-85°).

β -(3-keto-5-phenylpent- Δ^4 -enyl) indole (III).—Mannich base. HCl (I) (1 g.; 0.004 mole); indole (0.49 g.; 0.004 mole); water (50 ml.) Refluxed (8 hrs.). Solid. Crystallised from benzene; yellow needles; m.p. 127°C.; yield: 0.80 g. (65.5%).

Analysis: β -(3-keto-5-phenylpent- Δ^4 -enyl)-indole (III), $C_{19}H_{17}ON$, (mol. wt. 275), requires: C, 82.88; H, 6.22; O, 5.81 and N, 5.09%. Found: C, 82.16; H, 6.38; O, 6.29 and N, 5.34%.

I.R. bands at 3311 cm^{-1} (>NH), 1661 cm^{-1} (>CO).

α, α' -Di-(3-keto-5-phenylpent- Δ^4 -enyl)-pyrrole (IV).—Mannich base. HCl (I) (0.48 g.; 0.002 mole); pyrrole 0.97 g.; 0.001 mole); water (50 ml.).

Heated on water bath (3 hrs.). Oil extracted with ether. α, α' -Di-(3-keto-5-phenylpent- Δ^4 -enyl)-pyrrole (IV), crystallised from absolute ethanol. Yellow needles; m.p. 133°C; yield: 0.42 g. (97%).

Analysis: α, α' -Di-(3-keto-5-phenylpent- Δ^4 -enyl)-pyrrole (IV), $C_{26}H_{25}O_2N$ (mol. wt. 383) requires: C, 81.43; H, 6.57; O, 8.34; N, 3.65%. Found C, 81.08; H, 6.64; O, 8.61; N, 3.64%.

Infra-red absorption bands at 1605 cm^{-1} (>NH), 3344 cm^{-1} (>NH) and 1681 cm^{-1} (>CO).

N-(3-keto-5-phenyl pent- Δ^4 -enyl)-phthalimide (V). Mannich base (I) (0.48 g.; 0.002 mole); phthalimide (0.3 g.; 0.002 mole); water (20 ml.) Heated on water bath (10 hrs.). Oil. Extracted with ethyl acetate. Colourless prismatic needles from benzene. m.p. 140°. Yield: 0.48 g. (77.4%).

Analysis: *N*-(3-keto-5-phenyl-pent- Δ^4 -enyl)-phthalimide: (V) $C_{19}H_{15}O_3N$ (M.W. 305) requires: C, 74.74; H, 4.98; O, 15.72 and N, 4.59%. Found: C, 75.57; H, 5.06; O, 15.30 and N, 4.54%.

Infra-red bands at 1664 cm^{-1} (*tert* amide) and 1704 cm^{-1} (>CO).

α, α' -Di-(3-keto-5-phenyl-pentyl)-pyrrole (VI).—Mannich base (II) (1.5 g.; 0.007 mole.); pyrrole (0.25 g.; 0.0035 mole); water (30 ml.). Heated on water bath (20 hrs.). Oil isolated with ethyl acetate. Colourless microscopic needles from absolute ethanol. m.p. 88°C; yield: 1 g. (93%).

Analysis: α, α' -Di-(3-keto-5-phenyl-pentyl)-pyrrole (VI): $C_{26}H_{29}O_2N$ (mol. wt. 387) requires: C, 80.85; H, 7.54; O, 8.26 and N, 3.61%. Found: C, 81.14; H, 7.51; O, 8.10 and N, 3.63%.

Infra-red absorption bands at 3355 cm^{-1} (>NH); 1601 cm^{-1} (>NH) and 1706 cm^{-1} (>CO).

Di-(3-keto-5-phenyl-pentyl)-nitromethane (VII).—Mannich base (II) (1.4 g.; 0.006 mole); nitromethane (0.23 g.; 0.003 mole); water (25 ml.) Heated on water bath (25 hrs.) Oil isolated with ethyl acetate. Shinning colourless plates from absolute ethanol. m.p. 86°C. Yield 0.9 g. (92%).

Analysis: Di-(3-keto-5-phenyl-pentyl)-nitromethane. (VII) $C_{23}H_{27}O_4N$ (mol. wt. 381) requires: C, 72.42; H, 7.13; O, 16.78 and N, 3.67%. Found: C, 73.09; H, 7.15; O, 17.15 and N, 3.61%.

Infra-red bands at 1531 cm^{-1} ($-\text{NO}_2$) and 1704 cm^{-1} ($>\text{CO}$).

N-(3-keto-5-phenyl-pentyl)-phthalimide (VIII).—Mannich base (II) (0.5 g.; 0.0025 mole); phthalimide (0.36 g.; 0.0025 mole); water (25 ml.). Heated on water bath (8 hrs.). Semi-solid colourless needles from methanol, m.p., 102°C . yield, 0.52 g. (72%).

Analysis: *N*-(3-keto-5-phenyl-pentyl)-phthalimide (VIII); $\text{C}_{19}\text{H}_{17}\text{O}_3\text{N}$ (mol. wt. 307) requires: C, 74.25; H, 5.58; O, 15.62 and N, 4.56%. Found: C, 74.19; H, 5.74; O, 15.79 and N, 4.64%.

Infra-red bands at 1668 cm^{-1} (*tert* amide) and 1706 cm^{-1} ($>\text{CO}$).

Di-(3-keto-5-phenyl-pentyl)-cyanoacetamide (IX).—Mannich base (II), (0.418; 0.002 mole); cyanoacetamide (0.08 g.; 0.001 g.) and water (30 ml.). Heated on water-bath (8 hrs.). Solid. Colourless rods from dioxane m.p. 158°C . Yield: 0.3 g. (85%).

Analysis: *Di*-(3-keto-5-phenyl-pentyl)-cyanoacetamide (IX), $\text{C}_{25}\text{H}_{28}\text{O}_3\text{N}_2$ (mol. wt. 404) requires: C, 74.23; H, 6.98; O, 11.87 and N, 6.93%. Found: C, 73.57; H, 6.94; O, 12.46 and N, 7.14%.

N, N'-*Di*-(3-keto-5-phenyl-pentyl)-piperazine: (X).—Mannich base (II), (0.41 g.; 0.002 mole); piperazine. $6\text{H}_2\text{O}$, (0.2 g.; 0.001 mole); water (30 ml.) Heated on water bath (10 hrs.). Oil isolated with ethyl acetate. Colourless prisms from absolute ethanol, m.p. 80°C ; yield, 0.32 g. (80.5%).

Analysis: *N, N'*-*di*-(3-keto-5-phenyl-pentyl)-piperazine (X), $\text{C}_{26}\text{H}_{34}\text{O}_2\text{N}_2$ (mol. wt. 406) requires: C, 76.81; H, 8.43; O, 7.87 and N, 6.89%. Found: C, 76.67; H, 8.46; O, 8.04 and N, 7.01%.

1-(*N, N*-Dimethylamino)-3-keto-5-phenylpentane (II).—1-(*N, N*-Dimethylamino)-3-keto-5-phenylpent- Δ^4 -ene hydrochloride (4.0 g.) was taken up in ethyl alcohol (30 ml.) containing palladium on charcoal (prepared from 20 ml. of 1% palladium chloride solution on 2 g. charcoal) and hydrogenated. After the theoretical quantity of hydrogen had been absorbed about 400 ml. the product, 1-(*N, N*-dimethylamino)-3-keto-5-phenylpentane

hydrochloride was isolated in the usual manner; Hygroscopic; yield 4.0 g. (quantitative).

The free base was obtained by dissolving the base-hydrochloride in water, basifying with ammonium hydroxide. Isolation with ethylacetate, drying and removal of solvent gave the free base, 1-(*N, N*-dimethylamino)-3-keto-5-phenylpentane (II), b.p. 140°C , 4 mm.; 3.38 g.

Analysis: 1-(*N, N*-dimethylamino)-3-keto-5-phenylpentane, $\text{C}_{13}\text{H}_{19}\text{ON}$, requires C, 76.05; H, 9.33 and O, 7.72%. Found: C, 76.06; H, 8.86 and O, 7.67%.

The base is easily soluble in the usual laboratory solvents except light petroleum (b.p. $65\text{--}85^\circ\text{C}$).

Alkylation of KCN with 1-(N, N-dimethylamino)-3-keto-5-phenylpentane.—1-(*N, N*-dimethylamino)-3-keto-5-phenylpentane [(0.2 g.; 0.001 mole) was taken up in water (25 ml.) containing potassium cyanide (0.1 g. (excess)], heated on water bath (6 hours). Extraction with ethyl acetate; drying and removal of solvent gave: 1-cyano-3-keto-5-phenylpentane (XI) 0.06 g. Several crystallisations from ethanol gave m.p. $208\text{--}9^\circ\text{C}$.

Analysis: Calculated for 1-cyano-3-keto-5-phenylpentane $\text{C}_{12}\text{H}_{13}\text{ON}$ (mol. wt. 187): C, 76.97; H, 7.00; and N, 7.48%, Found: C, 76.47; H, 6.85 and N, 7.59%.

The alcoholic mother liquor gave an oil in very minute quantity which was purified by distillation at 0.2 mm. (b.p. could not be recorded). The product believed to be 1,10-diphenyl-3,8-diketo-6-cyano-decane (XII) requires: C, 79.50; H, 7.25; N, 4.03; O, 9.21. Calculated for $\text{C}_{23}\text{H}_{25}\text{O}_2\text{N}$, C, 79.25; H, 6.60, N, 4.63; O, 9.56%.

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