SOME ALKYLATION REACTIONS OF MANNICH BASES IN AQUEOUS MEDIUM

Part I.— Reactions of Phenyl-β-dimethylaminoethylketone and its Hydrochloride

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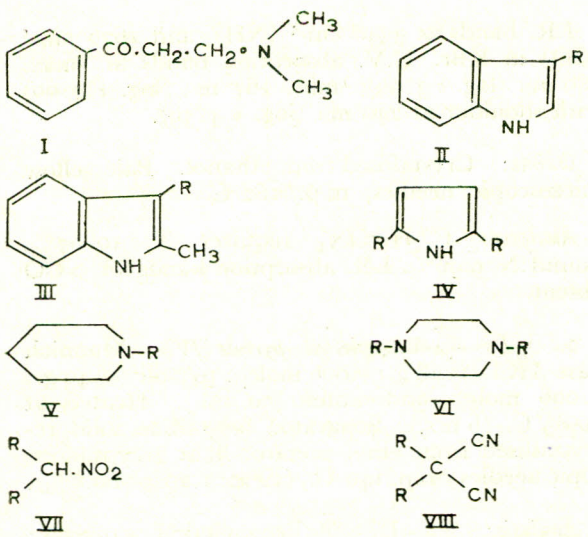
Alkylation reactions of the Mannich base: phenyl-β-dimethylaminoethylketone with indole, 2-methyl-indole, pyrrole, piperidine, piperizine, nitromethane and malononitrile in aqueous medium have been described.

Mannich bases have found a number of applications in organci syntheses. For instance heating or steam distillation gives ethylenic compounds as in the case of phenyl-β-dimethylaminoethylketone hydrochloride which gives Benzoylethylene.[1] β-Dimethylaminopropiophenone hydrochloride can be converted into benzoylpropionitrile by boiling with potassium cyanide in water.[2] In an earlier communication Kamal *et al.*[3] reported some alkylation reactions of Mannich bases in aqueous medium for the syntheses of some mono- and polyindolyl compounds. In the present communication the authors describe the reactions of the Mannich base: phenyl-β-dimethylaminoethylketone (I) or its hydrochloride in aqueous medium for the alkylation of suitable organic compounds having active methyl or methylene groups (as in nitromethane, methylcyanide, malonitrile etc.) or which can donate protons with ease as in the case of Indole (β-proton) or pyrrole (both α, α′ protons).



R = C_6H_5.CO. CH_2. CH_2

β-indolyl-propiophenone (II) has been prepared in three steps by the interaction of gramine methomethyl sulphate with the sodium derivative of ethyl benzoyl acetate [4] which gave ethyl skatylbenzoylacetate (95% yield: based on skatylmethomethyl sulphate) from which, on alkaline hydrolysis, β-indolyl-propiophenone was obtained (71% yield based on ethyl skatylbenzoylacetate).

When phenyl-β-dimethylaminoethylketone hydrochoride is refluxed with indole in water, β-indolylpropiophenone is obtained in 60% yield in one step. Reaction with the free base: phenyl-β-dimethylaminoethylketone gave the same product in very slightly higher yield (61%).

In a similar manner with 2-methylindole, β-(2-methyl-indolylpropiophenone) was obtained in 64% yield.

Alkylation of pyrrole with the Mannich base hydrochloride proceeded very smoothly on heating at 80-85°; giving as expected α, α′-dibenzoylethylpyrrole in 60% yield. Though evidence for α, α′ or (2,5-) substitutions is supplied indirectly by the diacetylation of pyrrole,[5] the N.M.R. data fully endorsed the view that the disubstitution was in fact in α, α′ or (2, 5). In $CDCl_3$ the N.M.R. Spectrum showed one superimposed AB system doublet centred at τ 4.12 (JAB 3C/Sec.) indicative of the two unsubstituted β, β protons in pyrrole under similar environment, confirming the structural assignment as shown in (IV). It further showed one singlet at τ 7.0 (eight protons of four methylene groups) and one multiplet centred at τ 2.52 (ten protons of two benzene rings). A further confirmation of disubstitution in the pyrrole ring is provided by its mass spectrum in which the parent peak is at m/e 331.

1,5-Dibenzoyl-3-nitropentane (VII) has been prepared by Norviko and co-workers [6] by the interaction of phenylvinylketone with nitro methane in the presence of a little sodiumethylate, in 52%

yield. It is also reported to have been prepared from chloropropiophenone by means of the Michael type addition with nitromethane at 0-8°C.[7]

Alkylation of nitro methane with the Mannich base hydrochloride gave the product: 1,5-dibenzoyl-3-nitropentane (VII) in 80% yield. Similar reaction with malononitrile gave 1,5-dibenzoyl-3, 3-dicyanopentane (VIII) m.p. 214°C. in about 54% yield.

Alkylation of piperidine and piperazine resulted in the replacement of the $-N<^{CH_3}_{CH_3}$ group for piperidyl and piperazinyl groups: N-(β-benzoylethyl)-piperidine (V) and N N′ Di-(β-benzoylethyl)-piperazine (VI) being obtained in 84% and 40% yield respectively—the reaction in the latter case completing in about 50 minutes. These two bases (V) and (VI) can be prepared through the normal Mannich reaction *viz.* through the interaction of acetophenone-formaldehyde and piperidine hydrochloride[8] (90% yield) or piperazine hydrochloride[9] (yield not recorded). The piperidine Mannich base (V) can also be prepared in 90% yield through the interaction of benzoylacetic acid, piperidine and formaldehyde.[9] This exchange of the end group containing nitrogen for another basic group to yield the corresponding Mannich base can be usefully employed for the preparation of some of the Mannich bases not obtainable in high yields through the direct method of their preparation.

Alkylation reactions of other Mannich bases already studied will form the subject of separate communications.

Experimental

All melting points are corrected. U.V. absorption spectra were determined with a Beckman Spectrophotometer Model D.K. 2 in 95% ethanol; I.R. Spectra were recorded with a Beckman I.R. 5; N.M.R. Spectra were determined on deutrochloroform solutions using tetramethylsilane as internal standard in a Varian A-60 spectrometer.

General Method.—The Mannich base hydrochloride (I) or free base where indicated, and the reactant to be alkylated were taken in water and the mixture heated under conditions described in each alkylation reaction. When the free base was employed ceasation in the evolution of dimethylamine was taken as indication of the completion of the reaction. The product if oily was isolated with ethyl acetate and if solid through filtration and crystallized from appropriate solvent.

β-*Indolyl-propiophenone* (*II*).—Mannich base HCl (1.28 g.; 0.006 mole), indole (0.70 g.; 0.006 mole), water (50 ml.). Refluxed on sand bath (9 hrs.). Separated crystalline solid recrystallised from ethyl acetate. Pale yellow diamond-shaped prisms. m.p. 126°C. (yield: 900 mg.; 60%). (Lit.[4] m.p. 126-27°C.).

Analysis: Calculated for: β-indolylpropiophenone: $C_{17}H_{15}ON$ (249): C, 81.90; H, 6.06; O, 6.42; N, 5.62%, Found: C, 81.99; H, 6.17; O, 6.52; N, 5.60%; Mol. Wt. (Rast), 251. I.R. bands at 3340 cm^{-1} (>NH) and 1674 (>CO) in KBr; U.V. absorption bands at λmax. 280 mμ (log. ε 4.74), 223 mμ (log. ε 4.35), λmin. 260 mμ (log. ε 3.96), 235 mμ (log. ε 4.35).

Oxime: Crystallised from ethanol; m.p. 170°C.

Analysis: $C_{17}H_{16}ON_2$ (264) requires N, 10.60%. Found: N 10.00%. I.R. absorption band for >CO absent.

β-(2-*methylindolyl*)-*propiophenone* (*III*).—Mannich base HCl (1.28 g.; 0.006 mole); 2-methylindole (0.78 g.; 0.006 mole); water (50 ml.). Refluxed on sand bath (9 hrs.) Crystalline solid–recrystallised from ethyl acetate. Yellow leaflets. m.p. 128°C. (yield: 970 mg.; 64%).

Analysis: β-(2-*methylindolyl*)-*propiophenone*.—$C_{18}H_{17}ON$-(263) requires: C, 82.10; H, 6.51; O, 6.08; N, 5.32%, Found: C, 81.42; H, 6.53;O, 6.29; N (by difference) 5.86% and Mol. Wt. (Rast) 289.

I.R. bands at 3348 cm^{-1} (NH) and 1672 cm^{-1} (CO) in KBr. U.V. absorption bands at λmax. 289 mμ (log. ε 3.99), λmin. 264 mμ (log. ε 4.00) with shoulder at 240 mμ (log. ε 4.39).

Oxime: Crystallised from ethanol. Pale yellow microscopic needles, m.p. 162°C.

Analysis: $C_{18}H_{18}ON_2$ requires N, 10.07%. Found:N, 9.96%. I.R. absorption bands for >CO absent.

2, 5-*Di*—(2-*benzoylethyl*)-*pyrrole* (*IV*).—Mannich base HCl (1.28 g.; 0.006 mole); pyrrole (0.40 g.; 0.006 mole) -and water (50 ml.). Heated at 80-85°C. (6 hrs.). Separated crystalline solid recrystallised from ethyl acetate; light grey microscopic needles; m.p. 140°C., (yield: 1.20 g.; 60.8%).

Analysis: 2,5 - Di - (2 - benzoylethyl) - pyrrole: $C_{22}H_{21}O_2N$, (331) requires: C, 79.73; H, 6.39; O, 9.66 and N, 4.23%. Found: C, 79.17; H, 6.27; O, 10.2; N, 4.36%. Mol. Wt. (Rast) 323.

I.R. absorption bands at 3348 cm-[2] (>NH) and 1682 cm-[1] (>CO) in KBr. U.V. absorption bands at: λmax. 278 mμ (log. ε 3.55), 241 mμ (log. ε 4.76) and λmin. 269 mμ (log. ε 3.51).

N-(β-benzoylethyl)-piperidine (*V*).—Mannich base HCl (1.28 g.; 0.006 mole); piperidine (1.02 g.; 0.012 mole) and water (50 ml.). Heated on water bath (50 hrs.). Oil b.p. 82°C. (0.6 m.m), $\eta_D^{29°}$ 1.545; (yield: 1.17 g.; 84%). Picrate m.p. 179°C. (Lit.[8] 180.5°C.). Mixed m.p. undepressed.

Analysis: Calculated for N-(β-benzoylethyl)-piperidine: $C_{14}H_{19}ON$, (217): C, 77.38; H, 8.81; O, 7.36; N, 6.45%. Found: C, 76.71; H, 8.53; O, 7.88 and N, 6.02%. Mol. Wt. (Rast) 211.

I.R. absorption bands (liquid film) at 3397 cm-[1] (>NH) and 1685 cm^{-1} (>CO).

N, N̄-Di(β-benzoylethyl)-piperazine (*VI*).—Mannich base HCl (0.64 g.; 0.003 mole); piperazine (0.58 g.; 0.003 mole) and water (50 ml.). Heated on water bath (50 mts.). Crystallised from dioxane. Yellow hexagonal plates. m.p. 144°C. (yield: 0.41 g.; 40%). Lit.[9] m.p. 141°C.

Analysis: Calculated for N, N̄-Di (β-benzoylethyl)-piperazine: $C_{22}H_{26}O_2N_2$ (350): C, 75.40; H, 7.48; O, 9.13 and N, 7.99%. Found: C, 75.34; H, 7.61; O, 9.30; N, 7.86%. Mol. Wt. (Rast), 340.

I.R. absorption bands at 1674 cm^{-1} (>CO) in KBr.

Dioxime: Crystallised from ethanol. Plates, m.p. 250°C. (dec.)

Analysis: $C_{22}H_{28}O_2N_4$ requires N, 14.81%. Found: N 13.13%.

1, 5-*Dibenzoyl-3-nitropentane*: (*VII*).— Mannich base HCl (1.28 g.; 0.006 mole); nitromethane (0.73 g.; 0.012 mole) and water (50 ml.). Refluxed on sand bath (9 hrs.). Crystalline solid recrystallised from ethyl acetate. Colourless microscopic needles. m.p. 134°C. (yield: 0.92 g.; 80%). Lit.[6] m.p. 132-133.5°C.

Analysis: Calculated for 1, 5-dibenzoyl-3-nitropentane: $C_{19}H_{19}O_4N$, (325): C, 70.14; H, 5.89; O, 19.67; N, 4.31%. Found: C, 70.30; H, 5.83; O, 19.81 and N, 4.51%.

I.R. absorption bands at 1354 cm^{-1} (>C.NO_2) and 1674 cm^{-1} (>CO) in KBr. U.V. absorption bands at λmax. 242 mμ (log. ε 4.53) and λmin. 269 mμ (log. ε 3.89).

Dioxime: Crystallised from ethanol. Colourless prismatic needles. m.p. 105°C. $C_{19}H_{21}O_4N_3$ requires:N, 11.8%; Found: N, 11.5%. I.R. absorbtion band for >CO absent.

1, 5-*Dibenzoyl-3-di-Cyano-pentane* (*VIII*).—Mannich base HCl (1.28 g.; 0.006 mole); malonitrile (0.79 g.; 0.012 mole) and water (50 ml.). Heated on water bath (9 hrs.). Crystalline solid recrystallised from ethyl acetate. Colourless prismatic needles m.p. 214°C. (yield: 1.02 g.; 54%).

Analysis: 1, 5-Dibenzoyl-3-cyano-pentane: $C_{21}H_{18}O_2N_2$ (330) requires: C, 75.45; H, 5.70; O, 10.05; N, 8.80%. Found: C, 76.23; H, 5.46; O, 6.72; N, 8.54% and Mol. Wt. (Rast) 316.

I.R. absorption band at 1672 cm^{-1} (>CO) in KBr. U.V. absorption bands at λmax. 245 mμ (log. ε 4.44) and λmin. 265 mμ (log ε 4.47) and 238 mμ (log. ε 4.38).

2:4-*Dinitro phenyl hydrazone*: crystallized from ethanol. Yellow prismatic needles. m.p. 222°C.; $C_{33}H_{28}N_{10}O_8$ requires: N, 22.3%; Found: N, 22.3% I.R. absorption band for >CO absent.

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