

ALKYLATION REACTIONS OF MANNICH BASES IN AQUEOUS MEDIUM

Part III.—Some Reactions of Gramine

AHMAD KAMAL, (MISS.) MUSARRAT ANJUM, (MISS.) SOORAIYA AZIZ AND ASADULLAH

Central Laboratories, Pakistan Council of Scientific and Industrial Research, Karachi

(Received April, 21, 1966)

Reactions of gramine with indole, 2-methylindole, pyrrole, pyrrolidine, piperidine, piperazine, isatin, cyclopentanone and cyclohexanone are described.

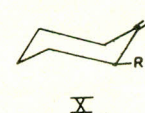
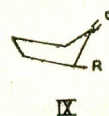
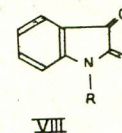
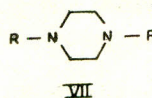
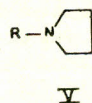
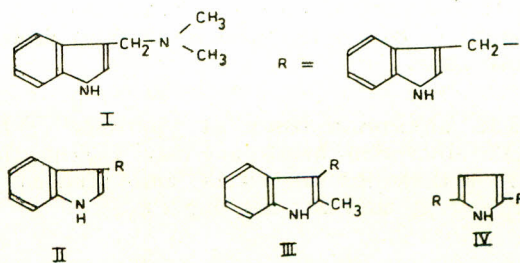
In earlier communications the authors have described the alkylation reactions of some Mannich bases viz. β -dimethylamino ethyl Ketone 1-(N, N-dimethylamino)-3-keto-5-phenyl Pent- Δ^4 -ene² 1-(N, N-dimethylamino)-3-keto-5-phenylpentane² and gramine³ in water as a general reaction. In the present communication further reactions of gramine as an alkylating agent in aqueous medium are presented.

Gramine (I) reacts with indole to yield di-indolylmethane (II), m.p. 158°C in 82% yield. Its identity was confirmed by comparison with an authentic sample of the product prepared by condensation of indole with formaldehyde.⁴ With 2-methyl indole the expected β (2-methylskatyl)-indole (III) is obtained in 84% yield. (m.p. 137°-38°C).

With pyrrole, as usual dialkylation at the α, α' position takes place, the product, α, α' -diskatyl-pyrrole (IV) being obtained in about 62% yield (m.p. 162-3°C).

With the bases, pyrrolidine, piperidine and isatin, the dimethylamino-moiety is exchanged giving the corresponding mono N-alkylated products, viz., N-skatyl pyrrolidine (V) (yield 77%; m.p. 125°C.), N-skatyl piperidine (VI) (yield 92%; m.p. 164°C) and N-skatylisatin (VIII) (yield 41%; m.p. 150-151°C) are obtained. With piperazine, an N-dialkylated product, N,N-diskatyl piperazine (VII) (yield about 48%; m.p. 222°C) is obtained in a similar manner.

In the alkylation of cyclopentanone and cyclohexanone 2-skatylcyclopentanone (IX) (yield 67.5%) and 2-skatylcyclohexanone (X) (yield 76%) are obtained as viscous liquids which failed to crystallise in our hand. They were, however, characterised through their oxime derivatives.



Experimental

All melting points are corrected. U.V. absorption spectra were determined with a Beckman spectrophotometer Model DK.2 in 95% ethanol. I.R. spectra were recorded with a Beckman I.R. 5.

GENERAL METHOD

Gramine (I) and the reactants to be alkylated were suspended in water and the mixture heated on water bath or refluxed on sand bath as indicated. After the completion of the reaction, the product, if oily, was isolated with ethyl acetate, and, if solid, through filtration and crystallised from an appropriate solvent.

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

Di-indolylmethane (II).—Gramine (0.52 g.; 0.003 mole), indole (0.35 g.; 0.003 mole) and water (50 ml.) were refluxed on a sandbath (30 hours). Crystalline solid extracted with ethyl acetate. Drying and removal of solvent gave light pink crystals. Yield, 0.61 g, 82%, m.p. 158°C; undepressed with an authentic sample of the material.⁴

Analysis: Calculated for di-indolylmethane: $C_{17}H_{14}N_2$ (246): C, 82.90; H, 5.73; N, 11.37%. Found: C, 82.93; H, 5.86; N, 11.35%. mol. wt. (Rast), 237.

I.R. absorption bands at 3390 cm^{-1} ($>NH$)
U.V. absorption bands at λ max. 282 $m\mu$ ($\log \epsilon$ 4.25) and 290 $m\mu$ ($\log \epsilon$ 4.18) and λ min. 247 $m\mu$ ($\log \epsilon$ 3.73) and 287 $m\mu$ ($\log \epsilon$ 3.4).

β - (2-methylskatyl) - indole. (III).—Gramine (0.52 g.; 0.003 mole), 2-methylindole (0.35g; 0.003 mole) and water (50 ml.) are refluxed on a sandbath (10 hours). The semisolid mass was extracted with ethylacetate. Drying and the removal of the solvent gave β -(2-methylskatyl) indole (III) which was crystallised from ethylacetate. Light brown leaflets, m.p., 137-8°C.; yield: 0.65g. (83.6%).

Analysis: β -(2-methylskatyl) indole, $C_{18}H_{16}N_2$ (260) requires C, 83.04; H, 6.20; N, 10.76%. Found: C, 83.04; H, 6.37; N, 10.78%. mol. wt. (Rast), 248.

I.R. absorption bands at 3390 cm^{-1} ($>NH$).
U.V. absorption bands at λ max. 247 $m\mu$ ($\log \epsilon$ 3.95) and λ min. 281 $m\mu$ ($\log \epsilon$ 4.59).

α, α' -Diskatylpyrrole (IV).—Gramine (0.52 g.; 0.003 mole), pyrrole (1.01 g.; 0.015 mole), and water (50 ml.) were heated on water bath (10 hours). The crystalline solid was crystallised from methanol. Light pink tiny globules, m.p., 162°C; yield: 0.6g (61.5%).

Analysis: α, α' -Diskatylpyrrole, $C_{22}H_{19}N_3$ (325) requires C, 81.20; H, 5.89; N, 12.91%. Found: C, 81.35; H, 5.85; N, 12.6%. mol. wt. (Rast), 231.

I.R. absorption bands at 3348 cm^{-1} ($>NH$).
U.V. absorption bands at λ max. 281 $m\mu$ ($\log \epsilon$ 4.24), 289 $m\mu$ ($\log \epsilon$ 4.02); min., 24 $m\mu$ ($\log \epsilon$ 3.89) 287 $m\mu$ ($\log \epsilon$ 3.91).

N-Skatylpyrrolidine (V).—Gramine (0.52 g.; 0.003 mole), pyrrolidine (0.40 g.; 0.06 mole)

and water (50 ml.) were heated on water bath (28 hours). Crystalline product. Recrystallised from dilute ethanol. Pale leaflets, m.p., 125°C. yield, 0.46g (77%).

Analysis: N-Skatylpyrrolidine, $C_{13}H_{16}N_2$ (200) requires, C, 77.96; H, 8.05; N, 13.99%. Found: C, 78.16; H, 8.6; N, 13.9%. mol. wt. (Rast), 206.

U.V. absorption bands at λ max. 279 $m\mu$. ($\log \epsilon$ 3.95); 289 $m\mu$ ($\log \epsilon$ 3.88); min., 238 $m\mu$ ($\log \epsilon$ 3.30) and 283 $m\mu$ ($\log \epsilon$ 3.8).

N-Skatylpiperidine. (VI).—Gramine (0.52 g.); 0.003 mole), piperidine (1.27 g.; 0.015 mole) and water (50 ml.) were heated on water bath (14 hours). The separated crystalline solid was crystallised from methanol, colourless leaflets; m.p. 164°C; yield, 0.59g; 92%).

Analysis: N-Skatylpiperidine, $C_{14}H_{18}N_2$ (214), requires C, 78.46; H, 8.47; N, 13.07%. Found: C, 78.64; H, 8.54; N, 13.21%. mol. wt. (Rast), 205.

U.V. absorption bands at λ max. 280 $m\mu$ ($\log \epsilon$ 4.2); 288 $m\mu$ ($\log \epsilon$ 4.0); λ min., 241 $m\mu$ ($\log \epsilon$ 3.7), 285 $m\mu$ ($\log \epsilon$ 4.1).

N, N'-Diskatylpiperazine (VII).—Gramine (0.52 g.; 0.003 mole), piperazine (0.58 g.; 0.003 mole) and water (50 ml.) were refluxed sandbath (2 hours). The separated crystalline solid was crystallised from methanol. Colourless diamond shaped crystals; m.p., 222°C, yield: 0.49 g; 47.6%.

Analysis: N, N'-Diskatylpiperazine, $C_{22}H_{24}N_4$ (mol. wt. 344) requires C, 76.71; H, 7.02; N, 16.27%. Found: C, 76.44; H, 7.21; N, 16.16%. mol. wt. (Rast), 331.

U.V. absorption bands at λ max. 280 $m\mu$ ($\log \epsilon$ 4.29); 288 $m\mu$ ($\log \epsilon$ 4.23); λ min., 241 $m\mu$ ($\log \epsilon$ 3.51); 286 $m\mu$ ($\log \epsilon$ 4.17).

N-Skatylisatin.—Gramine (0.52 g.; 0.003 mole), isatin (0.44 g.; 0.003 mole) and water (50 ml.) were refluxed (2 hours). The separated crystalline solid was crystallised from ethanol. Orange coloured hexagonal plates; m.p., 150-1°C; yield, 0.34 g (41%).

Analysis: N-Skatylisatin, $C_{17}H_{12}N_2O_2$ (mol. wt. 276) requires, C, 73.90; H, 4.38; O, 11.58 and N, 10.14%. Found: C, 73.41; H, 4.79; O, 11.71 and N, 10.01%. mol. wt. (Rast), 266.

I.R. absorption bands at 3333 cm^{-1} ($>\text{NH}$) and 1724 cm^{-1} ($>\text{CO}$). U.V. absorption bands at λ max: $245\text{ m}\mu$ ($\log\epsilon\ 4.18$), $281\text{ m}\mu$ ($\log\epsilon\ 3.71$), $287\text{ m}\mu$ ($\log\epsilon\ 3.70$). λ min. $232\text{ m}\mu$ ($\log\epsilon\ 3.98$), $250\text{ m}\mu$ ($\log\epsilon\ 4.13$); $260\text{ m}\mu$ ($\log\epsilon\ 3.64$) and $284\text{ m}\mu$ ($\log\epsilon\ 3.66$).

2-Skatylcyclopentaneone (IX).—Gramine (0.36 g.; 0.002 mole), cyclopentanone (0.17 g.; 0.002 mole) and water (25 ml.) were refluxed on a sandbath (35 hours). Extraction with ethyl acetate, drying and removal of solvent gave 2-skatylcyclopentanone as viscous oil, b.p. $160^\circ\text{C}/1\text{ mm}$. Yellow viscous oil. $[\mu]^{20^\circ\text{C}}\ 1.5910$ Yield 0.27 g. (67.5%). Failed to crystallise.

The product was characterised as oxime which crystallised from ethanol. Colourless needles. m.p., 156°C .

Analysis: 2-Skatylcyclopentanone oxime: $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}$ (228), requires C, 73.66; H, 7.06; N, 22.27; O, 7.01%. Found: C, 73.67; H, 7.01, N, 12.14 and O, 7.24%. mol. wt. (Rast), 220.

I.R. absorption bands at 3401 cm^{-1} ($>\text{NH}$) 3268 cm^{-1} ($-\text{OH}$) U.V. absorption bands at λ max. $282\text{ m}\mu$ ($\log\epsilon\ 4.01$); $290\text{ m}\mu$ ($\log\epsilon\ 3.95$); λ min. $288\text{ m}\mu$ ($\log\epsilon\ 3.93$); $250\text{ m}\mu$ ($\log\epsilon\ 3.63$).

2-Skatylcyclohexanone (X).—Gramine (0.36 g.; 0.002 mole), cyclohexanone (0.196 g.; 0.002 mole) and water (25 ml.) were refluxed on sand bath. (40 hours). Extraction with ethyl acetate, drying and removal of solvent gave 2-skatylcyclohexanone. Purified by distillation and the fraction distilling at $140^\circ/1\text{ mm}$. collected. Yellow vis-

cous oil which failed to crystallise in our hands; 0.32 g. (76%). $[\mu]^{20^\circ\text{C}}\ 1.5618$. Characterised as oxime which was obtained in the form of colourless prismatic needles from ethanol m.p., 208°C .

Analysis: 2 - Skatylcyclohexanone - oxime : $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}$ (242) requires: C, 74.35; H, 7.49; N, 11.56 and O, 6.60%. Found: C, 74.25; H, 7.43; N, 11.44 and O, 6.83%; mol. wt. (Rast), 210.

I.R. absorption bands at 3436 cm^{-1} ($>\text{NH}$); 3215 cm^{-1} ($-\text{OH}$) U.V. absorption bands at λ max. $290\text{ m}\mu$ ($\log\epsilon\ 3.88$) and $282\text{ m}\mu$ ($\log\epsilon\ 3.94$) λ min. $287\text{ m}\mu$ ($\log\epsilon\ 3.82$) $251\text{ m}\mu$ ($\log\epsilon\ 3.44$).

Acknowledgement.—The authors are thankful to Dr. R.A. Shah of the Microanalytical Division of these Laboratories and Dr. A. Bernhardt, Microanalytisches Laboratorium, Mulheim (Ruhr) for carrying out the analyses.

References

1. A. Kamal (Miss.) Sooraiya Aziz and (Miss.) Musarrat Anjum, Pakistan J. Sci. Ind. Res., **9**, 217 (1966).
2. A. Kamal and Asadullah, Pakistan J. Sci. Ind. Res., **9**, in press.
3. A. Kamal, A. Ali Quraishy and I. Ahmad, Tetrahedron, **19**, 681 (1963).
4. A. Kamal, A. Ali Quraishy, Tetrahedron, **19**, 513 (1963).
5. Strandtmann, Cohen et. al. J. Org. Chem., **30**, 3240 (1965).