A NEW ROUTE FOR SYNTHESIS OF 4(or 5) PROPYLIMIDAZOLE

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Abstract - Ethyl 1-ethyl-3-phthalimidoacetoacetate was prepared by condensation of ethyl 3-phthalimidoacetoacetate and acetaldehyde followed by reduction. The substituted acetoacetate was hydrolysed by dil.HCl and the corresponding aminoketone treated with potassium thiocyanate to yield 2-mercapto-4 (or 5)-propylimidazole. The later was oxidised to the corresponding imidazole.

Imidazole and its derivatives are of immense significance as they exhibit different biological activities[1-10], and therefore, it was thought worthwhile to extend the previous work[11, 12] on such derivatives from these laboratories. For preparation of 4 (or 5) propylimidazol, ethyl 3-phthalimidoacetoacetate[13] was condensed with acetaldehyde, employing Knoevenagel type of reaction, in equimolar amounts in presence of piperidine using sodium dried benzene as solvent, to yield ethyl ethylidene-3-phthalimidoacetoacetate (1) (m.p.75.5-76°; yield 60.5%). 1 was reduced by raney nickel to get ethyl 1-ethyl-3-phthalimidoacetoacetate (2), which was recrystallised from ethanol, m.p. 70°; yield 62%. (Found C 62.1; H 4.9; N 4.46. Calculated for $C_{16}H_{17}O_5N$ C, 63.3; H, 5.6; N, 4.41%). It is soluble in hot ethanol, glacial acetic acid, ether and benzene and gives a red colour with ferric chloride.

2 (7.6 g.) was hydrolysed with 30% HCl for 3 hours till the ester had dissolved. On cooling most of the phthalic acid was seperated. Precipitated phthalic acid was filtered and the filtrate was evaporated to dryness under reduced pressure. Highly hygroscopic hydrochloride of the aminoketone was obtained, which was dissolved in ethanol and precipitated with ether. The precipitate was quickly filtered and dissolved in water (10 c.c.). KCNS (3 g.), dissolved in water (4 c.c.) was then added and the mixture was heated on a water bath for two hours. It was slowly evaporated to dryness and the residue was dissolved

in warm water (50 c.c.) and treated with a saturated solution of mercuric acetate till the precipitation was complete. The light yellow coloured precipitation was complete. The light yellow coloured precipitate of mercury complex of 2-mercapto-4 (or 5) n-propylimadazole was suspended in water (25 c.c.), made acidic with HCl (dil.), and H_2S gas passed. Mercury sulphide was filtered and washed twice with 5 c.c. portions of water. The combined filterate and washings were treated with charcoal and filtered. The clear filterate was evaporated to dryness when hydrochloride of 2-mercapto-4 (or 5) n-propylimidazole (3) was obtained as a yellowish white, hygroscopic substance. This was dissolved in dry ethanol and neutralised with alcoholic KOH. Precipitated KCl was filtered and the filterate concentrated for crystallisation, m.p. 183.5°, yield 2.4 g. (Found N, 19.22, S, 22.61 calculated for $C_6H_{10}N_2S$ N, 19.72; S, 22.54%).

3 was oxidised by ferric chloride (26 g.) when 4 (or 5) n-propyl imidazole(4), m.p. 66.8°, was obtained in quantitative yield. (Found C, 66.1; H, 9.28; N, 25.99 calculated for $C_6H_{10}N_2$ C, 65.46; H, 9.09; N, 25.45%). Hydrochloride m.p. 120°; picrate, m.p. 178.5°. Structure was further confirmed by comparing with authentic sample[12] (m.p. 66.6°).

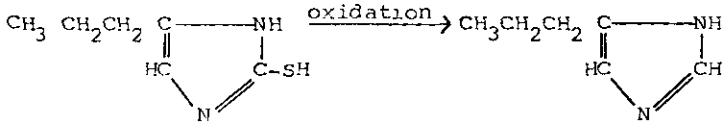
Thus for the first time the ester 1 has successfully been utilized to prepare 4 (or 5) n-propylimidazole in excellent yield and the procedure can schematically be represented as follows :

$$C_6H_4(CO)_2NCH_2CO\ CH_2\ COO\ C_2H_5 + CH_3CHO \xrightarrow[\text{benzene}]{\text{piperidine}} C_6H_4(CO)_2NCH_2CO\ \underset{\underset{CH.CH_3}{\|}}{C}\ COOC_2H_5$$

1

$$\xrightarrow{\text{Raney Ni}} C_6H_4(CO)_2N\ CH_2CO\ \underset{\underset{CH_2CH_3}{|}}{CH}\ COOC_2H_5 \xrightarrow{30\%\ HCl} CH_3CH_2CH_2CO\ CH_2NH_2 \xrightarrow{KCNS}$$

2



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Acknowledgement - Authors are thankful to CSIR, New Delhi for financial assistance provided.

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Received, 18th July, 1979