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A NEW METHOD FOR SYNTHESIS OF N-METHYL-1(2H)ISOQUINOLONES - A NEW REACTION OF HOMOPHTHALIC ACID WITH VILSMEIER REAGENT

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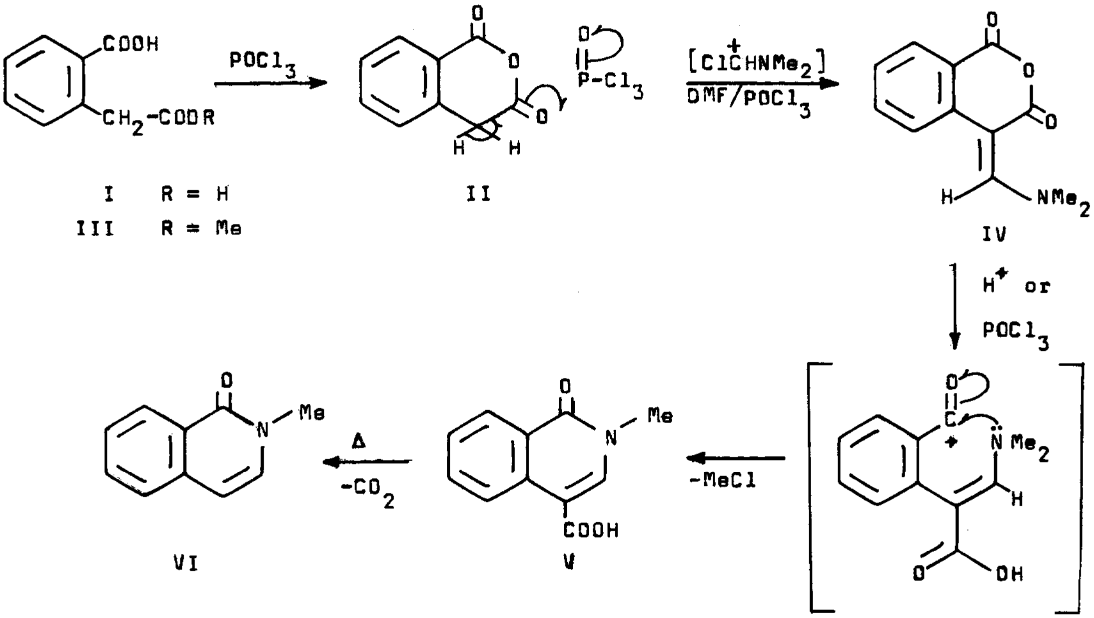
Vilsmeier reagent (DMF/$POCl_3$) reacted with homophthalic acid (I) on boiling water bath to give the known N-methyl-4-carboxy-1(2H)isoquinolone (V) in excellent yield nearing 80% of theory, [m.p. 262-63°, Lit.[1] m.p.262°. Found C, 66.3; H, 4.8; N, 6.9. $C_{11}H_9O_3N$ requires C, 66.6; H, 4.4; N, 6.9 %. UV. λ_{max}^{MeOH} 220, 295, 330 nm, log ε 4.3, 4.0, 3.7. IR. ν_{max}^{Nujol} 1650 (broad, >C=O of lactam and of COOH), 1620 (>C=C<), 1490 (aromatic) cm^{-1}. ^1H-NMR (60 MHz, CF_3COOH) δ 3.85 (s, 3H, N-C$\underline{H}_3$), 7.85 (m, 2H, H-6 and H-7), 8.5 with a spliting near base at 8.6 (2H, H-3 and H-5 overlapped), 8.92 (d, 1H, H-8, J = 7Hz) ppm]. The carboxyisoquinolone (V) decarboxylated smoothly in nearly quantitative yield by heating it in a metal bath above its m.p. (265-70°) to give the known N-methyl-1(2H)isoquinolone (VI) [m.p. 38-40°, Lit.[2,3,4] m.p. 38-40°; Found C,75.5; H, 5.7; N, 6.1; $C_{10}H_9ON$ requires C, 75.5; H, 5.7; N, 6.1 %. UV. λ_{max}^{MeOH} 225, 285, 325 nm, log ε 4.2, 3.9, 3.7. IR. ν_{max}^{Nujol} 1630 (>C=O of lactam), 1610 (>C=C<) and 1590 (aromatic) cm^{-1}. ^1H-NMR (60 MHz, $CDCl_3$) δ 3.55 (s, 3H, N-C$\underline{H}_3$), 6.42 (d, 1H, -CH=C$\underline{H}$-N, J = 7.5 Hz), 7.08 (d, 1H, C$\underline{H}$=CH-N, J = 7.5 Hz), 7.55 (m, 3H, H-5, H-6 and H-7), 8.5 (m, 1H, H-8) ppm]. The identity of V was further confirmed by preparing the known ethyl ester[1] (m.p. 98°). UV, IR and NMR spectra are recorded for the first time.

The present synthesis for V and VI excel in all respects from those available for them[2,3,4]. An excellent new reaction is thus made available which will be very useful for achieving synthesis of many isoquinolone alkaloids recently isolated[5]. The isoquinolones are also known for their medicinal importance[6].

The reaction with Vilsmeier reagent was applied to homophthalic anhydride (II) and to methyl 2-carboxyphenylacetate (III) at boiling water bath temperature when V was obtained in both the cases in excellent yield. Further investigation showed that at lower temperature ($\sim 0°$) I,II as well as III reacted with Vilsmeier reagent to give in excellent yield, 4-(N,N-dimethylaminoformylidene)-isochroman-1,3-dione IV [m.p. 144-45°. Found C, 66.8; H, 5.5; N, 6.8. $C_{12}H_{11}O_3N$ requires C, 66.3; H, 6.1 and N, 6.8 %. UV. λ_{max}^{MeOH} 225, 275, 370 nm log ε 4.2, 3.9, 4.0. IR. ν_{max}^{Nujol} 1720, 1680 (>C=O twin bands of anhydride), 1570 (>C=C<), 1610 (aromatic) cm^{-1}. ^1H-NMR (60 MHz, $CDCl_3$) δ 3.37 (s, 6H, $-N-(CH_3)_2$), 7.35 (m, 3H, H-7, H-6 and H-5), 7.95 (s, H, $-CH-NMe_2$), 8.15 (m, 1H, H-8) ppm]. Its constitution was evident from the spectral data.



The isochroman-dione IV on heating with $POCl_3$ alone or with $DMF/POCl_3$ on boiling water bath gave V that showed the course of the reaction. The reaction may then be formulated for II as given above. The formation of IV by the action of $DMF/POCl_3$ at 0° on I and III suggests that they get initially converted into II. Rearrangement seems to have been promoted by coordination of the oxygen of the anhydride ring of IV with proton or $POCl_3$.

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References :

1. W. Dieckman and W. Meiser, Chem. Ber., 41 : 3267 (1908).
2. E. Bamberger and W. Frew, Chem. Ber., 27 : 205 (1894).
3. H. Decker, J. pr. Chem., 47 : 28 (1893).
4. N.I. Fisher and F.M. Hammer, J. Chem. Soc., 1907 (1934).
5. S.W. Pelletier, 'Chemistry of the Alkaloids', Von Nostrand Reinhold Company (1970), p. 77.
6. T.S. Sulkowski and M.A. Willie, US Pat., 3,452,027, 24 June 1969; Chem. Abstr., 71 : 112830 (1969).