Synthesis of dibenzo[b,h][1,6]naphthyridin-5,6-diones

M Sekar & K J Rajendra Prasad*
Department of Chemistry, Bharathiar University,
Coimbatore 641 046, Tamil Nadu, India
Received 12 March 1999; accepted 4 June 1999

The attempted synthesis of 4-hydroxy-3-(3'-methyl-1'-oxo-2'-butenyl)quinoline-2(1H)-ones 3, desired precursors for flindersine 4, khaplafoline 5 and their derivatives, resulted in a dimerization reaction leading to dibenzo[b,h][1,6]naphthyridin-5,6-diones 6. A mechanism is suggested to explain this reaction.

The reaction of diethyl 2-(3'-methyl-but-2'-enyl)malonate with anilines has been used as a general method of synthesis of 3-(3',3'-dimethylallyl)-4-hydroxy-2-quinolinones 1-4. As a corollary to the above realization, of the synthesis of 4-hydroxy-3-(3'-methyl-1'-oxo-2'-butenyl)quinolin-2-ones 3 and from them the 2,2-dimethyl-2H-pyran-2,3-c]quinolin-2-ones 4 and/or 2,2-dimethyl-2H-pyran-2,3-b]quinolin-5-ones 5, which are well-represented among the alkaloids of the Rutaceae 5, we were interested in extending the synthetic programme to the naturally occurring derivatives, viz., pyrans group of alkaloids. Diethyl 2-(3'-methyl-1'-oxo-but-2'-enyl)malonate 2 obtained from diethyl malonate and dimethyl acryloyl chloride on treatment with aniline 1 in boiling diphenyl ether as a plausible means to derive the 4-hydroxy-2-quinolinone derivative 3, as a precursor to pyran alkaloids (4,5) furnished a yellow solid product on work-up. Recrystallisation from benzene-ethyl acetate mixture furnished pale yellow crystals, m.p. 286°; yield 75%.

The analytical values are compatible with the molecular formula C_{16}H_{12}N_{2}O_{2} (as that of 6a). The IR spectrum showed an NHCO band at 1650 cm\(^{-1}\), a free CO band at 1630 cm\(^{-1}\) and the NH band at 3250 cm\(^{-1}\). But the spectrum lacked the absorption expected of a 3-methyl-4-butenoxy group in the region 1360-1380 cm\(^{-1}\). \(^{1}H\) NMR spectrum of the compound taken in dimethyl sulfoxide also did not register the presence of such a butenyl group 6-10, but showed instead a 8-proton multiplet in the aromatic region (\(\delta\) 7.00-7.80). The mass spectrum showed molecular ion peak at \(m/z\) 262 (85%). On the basis of these spectral data, we inferred that a dimeric product of the type 6a emanated from the reaction.

The reaction course apparently showed that the quinolinone 3 might have cyclised via internal Michael addition of the 4-hydroxy group to the side chain olefinic bond to yield the tricyclic derivative 7. This compound might then undergo retro Diels Alder reaction at the high temperature to yield the "quinone" type of compound 8. Addition of aniline to 8 yields the intermediate 9 which is capable of cyclisation to the tetracyclic compound 10 followed by aromatisation readily to 6. It is pertinent to mention here that the reaction of aniline on ketene...
carbonyl is ruled out on the basis of the formation of more stable aromatised product 6.

Experimental Section

Melting points were determined either on Boetius microbeating table or on Mettler FP5 apparatus and are uncorrected. IR spectra was recorded on a Perkin-Elmer-597 spectrophotometer, NMR-spectra on Varian EM-390 (90 MHz) instrument and mass spectra on Jeol JMS300 spectrometer. Microanalyses were performed on Carlo Erba-1106 or Perkin-Elmer-240 B CHN analyser.

Preparation of diethyl-2-(3'-methyl-1'-oxo-but-2'-enyl)malonate: General procedure. A mixture of 3.84 ml of sodium and 15 mL of dry ethanol was stirred in a three necked flask. After the sodium ethoxide had formed completely, 4 g (0.025 mole) of diethylmalonate was added during 30 min. After all the diethylmalonate had been added, the mixture was heated on a water bath for 15 min and allowed to cool. Dimethylacryloyl chloride (5.9 g, 0.05 mole) was then added over a period of half an hour. This was heated on a water bath for 3 hr, to complete the reaction. The flask was set up for distillation to distill off ethanol. The residue was diluted with water and extracted with ether. The etheral extract was washed with water and dried over anhyd. Na₂SO₄ and filtered. The filtrate was then concentrated to give diethyl 2-(3'-methyl-1'-oxo-but-2'-enyl)malonate. It was purified by distillation, b.p. 152°C; yield 5.44 g (80%).

Reaction of aniline and diethyl 2-(3'-methyl-1'-oxo-but-2'-enyl)malonate: Preparation of dibenzo[b,h][1,6]naphthyridin-5,6-diones 6. Diethyl 2-(3'-methyl-1'-oxo-but-2'-enyl)malonate and aniline derivatives (1, 0.1 mole) were dissolved in redistilled diphenylether (10 mL) and heated to reflux under nitrogen for 5 to 6 hr. The diphenylether was removed by distillation and the residue was treated with hexane. The insoluble material was filtered off, washed with water and recrystallised from glacial acetic acid to furnish 6 as yellow needles.

Dibenzo[b,h][1,6]naphthyridin-5,6-diones 6a: m.p. 286-87°C Anal. Found: C, 73.28; H, 10.64; N, 3.86. Calc. for C₁₈H₁₈N₂O₂: C, 73.27; H, 10.67; N, 3.84%. MS: m/z 262 (M⁺); IR (KBr): 3250 (NH), 1650 (NHCO) and 1630 (CO) cm⁻¹; PMR (DMSO-d₆) δ 7.00-7.80 (m, 8H, C₈-H, C₉-H, C₁₀-H, C₁₁-H).

1,8-Dimethoxy-dibenzo[b,h][1,6]naphthyridin-5,6-diones 6b: m.p. 275-76°C. Anal. Found: C, 67.10; H, 4.35; N, 8.66. Calc. for C₁₈H₁₈N₂O₂: C, 67.07; H, 4.37; N, 8.68%. MS: m/z 322 (M⁺); IR (KBr): 3400 (NH), 1680 (NHCO), 1640 (CO) cm⁻¹; PMR (DMSO-d₆) δ 3.60 (s, 6H, C₁-, C₈-OCH₃), 6.80-7.90 (m, 6H, C₂-H, C₃-H, C₄-H, C₅-H, C₆-H, C₉-H, C₁₁-H) and 9.90 (s, 2H, 2NH).

2,9-Dimethyl-dibenzo[b,h][1,6]naphthyridin-5,6-diones 6c: m.p. 290-91°C. Anal. Found: C, 74.50; H, 4.88; N, 9.68. Calc. for C₁₈H₁₈N₂O₂: C, 74.47; H, 4.86; N, 9.64%. MS: m/z 290 (M⁺); IR (KBr): 3350 (NH), 1680 (NHCO), 1650 (CO) cm⁻¹; PMR (DMSO-d₆) δ 2.20 (s, 6H, C₂-H, C₃-H, C₄-H, C₅-H, C₆-H, C₇-H, C₈-H, C₁₁-H) and 9.80 (s, 2H, 2NH).

1,8-Dimethyl dibenzo[b,h][1,6]naphthyridin-5,6-diones 6d: m.p. 282-83°C. Anal. Found: C, 74.49; H, 4.84; N, 9.62. Calc. for C₁₈H₁₈N₂O₂: C, 74.47; H, 4.86; N, 9.64%. MS: m/z 290 (M⁺); IR (KBr): 3300 (NH), 1660 (NHCO), 1640 (CO) cm⁻¹; PMR (DMSO-d₆) δ 2.20 (s, 6H, C₂-H, C₃-H, C₄-H, C₅-H, C₆-H, C₇-H, C₈-H, C₉-H, C₁₁-H).

Acknowledgement

We thank RSIC, CDRI Lucknow and SIF, JISC, Bangalore for the analysis, mass and NMR spectra. M.S. thank the CSIR, New Delhi, India, for the award of Senior Research Fellowship.

References