Arch. Pharm. Res. Vol. 18, No. 1 pp. 27-30, 1995

Synthesis of Some Pyridine and Dihydropyridine Derivatives from 7-Hydroxy-8-Methoxy-2-Oxo-2H-1-Benzopyran-6-Carboxaldehyde

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(Received May 20, 1994)

The Hantzsh reaction of 7-hydroxy-8-methoxy-2-oxo-2H-1-benzopyran-6-carboxaldehyde (1) with ethyl acetoacetate and ammonia yields the dihydropyridine derivative 2 together with the pyridine derivative 3 and the eight membred ring derivative 4. Reaction of 1 with ethyl cyanoacetate and malononitrile gives the iminodicoumarin derivatives 5 and 6 respectiely. The latter compound was reacted with butan-2-one and acetophenone to produce the Michael adduct 7a, b and the 2-aminopyridine derivatives 8a, b.

Key words: Hantzsh reaction, Coumarins, Benzopyrancarboxaldehyde, Dihydropyridine, Pyridines

INTRODUCTION

Substituted coumarins are regarded as an important class of compounds. They are known to be anticoagulants (Desheesh *et al.*, 1987; Esmon *et al.*, 1987), to have cytostatic activity (Gawron *et al.*, 1987), and exhibit antithrombotic and antimetastatic efficacy (Smith *et al.*, 1988).

Also, 1,4-dihydropyridine derivatives are pharmaceutically important compounds (Lednicer *et al.*, 1980). Our goal is to synthesize new comarin derivatives having the 1,4-dihydropyridine ring or other heterocyclic rings which might have interesting pharmacological properties.

MATERIALS AND METHODS

All melting points were uncorrected. The infra red spectra were recorded on a Unicam SP 1000 Spectrophotometer. The p.m.r. spectra were run on a Varian (M-390 spectrometer at 90 or 200 MHz), using TMS as internal standard in $CDCl_3$ or DMSO. mass spectra were recorded on mass spectrometers MS 30 and M59 (AEL) at 70 eV.

Preparation of Compound 1

Compound 1 was obtained by the ozonolysis of xanthotoxin (Brokke *et al.*, 1958).

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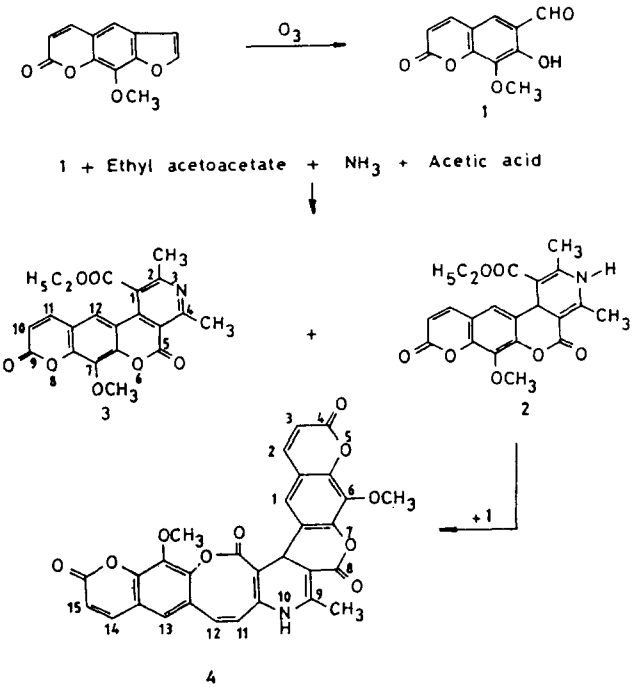
Procedure of the Reaction of 1 with Ethyl Acetoacetate and Ammonia

To a suspension of 1 (0.01 mole) in ethyl acetoacetate (0.01 mole), 3 ml glacial acetic acid and 6 ml ethanol, 1 ml ammonia is added. Then 3 ml glacial acetic acid are added again. The reaction mixture is heated at 90℃ until it dissolves and 1 ml ammonia is added. The reaction mixture is refluxed for 4 hrs. A small amount of precipitate is formed which is filtered and discarded. Ether is added to the filtrate, yellow crystals are formed which are a mixture of compounds 2 and 4. They are separated by boiling in glacial acetic acid: compound 4 (m.p. 240) dissolves and compound 2 is obtained pure since it is in soluble, m.p. 220℃, yield ca. 8% (Found: C, 63.65, H, 4.43, N, 3.52, $C_{21}H_{18}NO_7$ requires C, 63.67, H, 4.45, N, 3.53%); MS (m/e): 395 $(M\text{-}H^+)^+$, 367 $(M\text{-}CO)^+$, 323 $(M\text{-}COOC_2H_5)^+$, IR (cm^{-1}); 3540, 3490, 3438 (NH), 1734, 1730, (coumarin C=O), 1720 (ester C=O).

Evaporating the acetic acid, 4 is obtained in pure from, m.p. 240℃ ca. 20% (Found: C, 46.98, H, 3.42, N, 2.50, $C_{30}H_{19}NO_{10}$ requires C, 65l.10, H, 3.44, N, 2.53%). ^1H NMR ($CDCl_3$+DMSO, 200 MHz), 7.98-7.96 (d, 1H, J=8 Hz, H_6), 7.9-7.92 (d, 2H, J=8 Hz, H_{15} and H_{25}), 7.75 (s, 2H, H_{11} and H_{19}), 7.15 (s, 1H, D_2O exchangeable NH), 6.22-6.25 (d, 1H, J=8 Hz, H_7), 6.06-6.05 (d, 2H, J=8 Hz, H_{16} and H_{26}), 4.0 (s, 1H, H_3), 3.56 (s, 6H, $2OCH_3$), 2.5 (s, 3H, CH_3). ^{13}C NMR (DMSO): 170.01, 169.12, 163.45, 160.51 (C_{10}, C_{24}, C_{17}

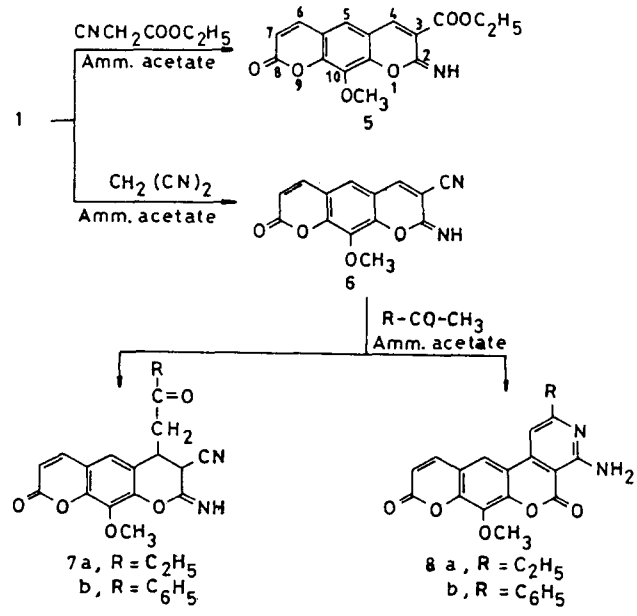


and C_{27}), 159.82, 158.82, 153.11 and 149.22 (C_{13}, C_9, C_{21} and C_{23}). 147.94 (C_1), 145.80 (C_5), 144.8 (C_{15}), 144.37 (C_{25}), 140 (C_{14}), 135.38 (C_{22}), 133.5 (C_2), 129.31 (C_4), 124.61, 123.72, 121.01, 115.51 (C_{20}, C_{18}, C_{12}), 117.17 (C_6), 111.7 (C_7), 1115.51, 111.11 (C_{19} and C_{11}), 108.92, 107.81 (C_{16}, C_{26}), 60.90, 61.64 ($2OCH_3$), 26.67 (C_8), 22.79 (CH_3); IR(cm^{-1}): 3580, 3440, 3240 (NH), 1740, 1730 (coumarin C=O), 1720 ester C=O).

Evaporating the filtrate of 2 and 4 in ether and crystallizing the solid obtained from acetone, 3 is separated as light yellow crystals, m.p. 240°C, yield ca. 20% (Found: C, 63.77, H, 4.29, N, 3.52, $C_{21}H_{17}NO_7$ requires C, 63.80, H, 4.30, N, 3.54%). 3 was found to be different from 4 by TLC and mixed m.ps. ^{1}H NMR ($CDCl_3$, 200 MHz): 8.45 (s, 1H, H_{12}), 7.8-7.9 (d, 1H, J=8 Hz, H_{11}). 64-6.5 (d, 1H, J=8 Hz, H_{10}), 4.4-4.55 (q, 2H, J=8 Hz, *CH_2CH_3), 4.2 (s, 3H, OCH_3), 2.8 (s, 3H, CH_3), 2.7 (s, 3H, CH_3), 1.4-1.5 (t, 3H, J=8 Hz, CH_2*CH_3); IR(cm^{-1}) 1760, 1735 (coumarin C=O), 1720 (ester C=O) 1630 (C=N).

The 2-iminodicoumarin derivative (5)

A mixture of 1 (0.01 mole) and ethyl cyanoacetate (0.01 mole) in absolute ethanol (10 ml) and few drops piperidine are refluxed for 5 hrs. The solvent is evaporated under reduced pressure and the solid obtained is crystallized from abs. ethanol and recrystallized from chloroform, m.p. 25°C, yield ca. 80% (Found: C, 60.74, H, 3.91, N, 4.33, $C_{16}H_{13}NO_7$ requries C, 60.95, H, 4.13, N, 4.44%). ^{1}H NMR (DMSO, 90 MHz): 8.75 (s, 1H, H4), 8.04-8.13 (d, 1H, J=10 Hz, H_6), 7.97 (s, 1H, H_5), 6.46-6.57 (d, 1H, J=10 Hz), 4.16-4.41 (q, 2H, J=7 Hz,



CH_2), 4.00 (s, 3H, OCH_3), 1.2-1.35 (t, 3H, J=7 Hz, CH_3): IR(cm^{-1}): 3300, 3600 (NH), 1780 (coumarin C=O), 1750 (ester C=O), 1630 (C=N).

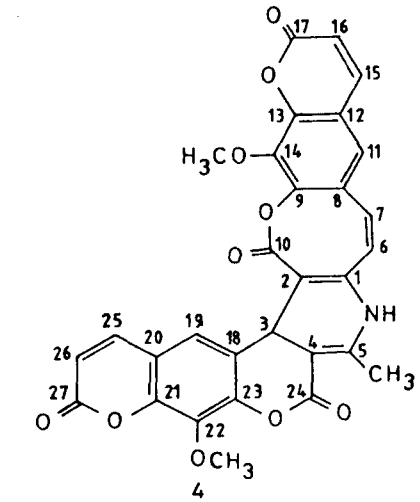
2-Imino-3-Cyanodicoumarin Derivative (6)

A mixture of compound 1 (0.01 mole) and malononitrile (0.01 mole) in absolute ethanol (10 ml) and ammonium acetate (0.5 g) are refluxed for 10 min. A white precipitate is formed during the reaction which is filtered and crystallized from cold chloroform-acetone to give 6, m.p. 255°C, yield ca. 90% (Found: C, 63.62, H, 3.00, N, 10.57, $C_{14}H_8N_2O_4$ requires C, 63.64, H, 3.03, N, 10.61%). ^{1}H NMR (DMSO, 200 MHz): 8.95 (s, 1H, H_4), 8.1-8.2 (d, 1H, J=9 Hz, H_6), 7.9 (s, 1H, H_5), 6.5-6.6 (d, 1H, J=9 Hz, H_7), 4.0 (s, 3H, OCH_3); MS (m/e): 269 (M^+); IR(cm^{-1}); 3400-3600 (NH), 2220 (C≡N), 1740 (C=O), 1620 (C=N).

Procedure for the Reaction of 6 with Ethyl Methyl Ketone

Compound 6 (0.08 mole) is refluxed with excess ethyl methyl ketone (0.5 g) and 25 ml absolute ethanol for 1 hr. The solvent is evaporated under reduced pressure. The precipitate obtained is crystallized from chloroform and ethanol and few drops of ether to give yellow crystals (7a) m.p. 232°C, yield ca. 30% (Found: C, 62.72, H, 4.52, N, 8.29, $C_{18}H_{16}N_2O_5$ requires C, 63.53, H, 4.71, N, 8.24%).

The filtrate is evaporated and crystallized from glacial acetic acid to give 8a, m.p. 240°C, yield ca. 35% (Found: C, 64.32, H, 3.69, N, 8.75, $C_{18}H_{12}N_2O_5$ requires C, 64.29, H, 3.57, N, 8.33%); ^{1}H NMR (DMSO, 200 MHz): 8.7 (s, 1H, H_1), 7.97-8.05 (d, 1H, J=8 Hz, H_{11}), 7.9 (s, 1H, H_{12}), 6.43-6.48 (d, 1H, J=8 Hz, H_{10}), 4.28-



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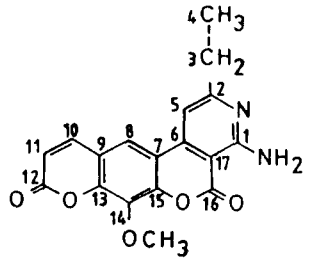

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^{13}C NMR numbering

4.32 (q, 2H, J, J=4 Hz, CH_2), 4.4 (s, 3H, OCH_3), 1.3-1.35 (t, 3H, J=4 Hz, CH_3); ^{13}C NMR (DMSO): 16.93 (C_{12}), 158.14 (C_{16}), 154.7 (C_{13} and C_{15}), 149.82 (C_2), 149.03 (C_1), 148.21 (C_{10}), 143.47 (C_2), 133.23 (C_{14}), 124.3 (C_8), 116.86 (C_5), 116.47 (C_{17}), 116.15 (C_9 and C_7), 115.72 (C_{11}), 61.45 (OCH_3), 28.92 (C_3), 13.86 (C_4); IR (cm^{-1}): 3400-3600 (NH_2), 1720-1740 (coumarin C=O), 1620 (C=N).

Procedure for the Reaction of 6 with Acetophenone

The same procedure used for the reaction of 6 with ethyl methyl ketone is used for its reaction with acetophenone. A precipitate is obtained from the reaction mixture after being cooled which is filtered and washed with ethanol to give dark crystals 7b, m.p. 250°C, yield ca. 60% (Found: C, 67.71, H, 3.19, N, 7.45, ($C_{21}H_{12}N_2O_5$ requires C, 67.74, H, 3.24, N, 7.53%); ^1H NMR (DMSO, 90 MHz): 6.44-8.44 (m, 8H, 6 arom. $H_5+H_6+H_7$), 6.2-6.42 (d, 1H, J=9 Hz, H_7), 4.4-4.8 (m, 2H, H_3+H_4), 3.9 (d, 2H, J=2 Hz, CH_2), 3.88 (s, 3H, OCH_3): IR(cm^{-}): 3340, 3200 (NH), 2220 (C≡N), 1740 (coumarin C=O), 1660 (C=O), 1620 (C=N).

The filtrate is evaporated and crystallized from dil, ethanol and few drops of acetone to give 8b, m.p. 70°C, yield ca. 65% (Found: C, 68.02, H, 4.00, N, 7.19, $C_{22}H_{14}N_2O_5$ requires C, 68.39, H, 3.63, N, 7.25%), MS (m/e): 385 $(M\text{-}H^+)^+$; IR(cm^{-1}): 3600-3400 (NH_2), 1740-1720 (coumarin C=O), 1620 (C=N).

RESULTS AND DISCUSSION

The Hantzsh reaction (O callagan *et al.*, 1987; Svetlik *et al.*, 1987) of 1-hydroxy-8-methoxy-2-oxo-2H-1-benzopyran-6-carboxaldehyde (1) with ethyl acetoacetate and ammonia in glacial acetic acid at reflux temperature produces the dihydropyridine derivative 2 which spontaneously oxidizes to yield the pyridine derviative 3. Compound 2 can react in the reaction mixture with another molecule of 1 to give an eight membered ring condensation product 4. Effectively three products for this reaction 2, 3 and 4 were separated and characterized.

The 1,4-dihydropyridine derivative 2 was sparingly soluble in NMR solvents but its structure was proved by mass spectrum which showed a molecular ion at m/e 395 $(M\text{-}H^+)^+$.

The structure of the eight membered ring derivative 4 was based mainly on its ^{13}C NMR which showed 30 peaks corresponding to the 30 carbon atoms present. Its ^1H NMR spectrum showed the peaks of the olefinic protons H_7 and H_6 at 6.22-6.25 and 7.98-8.0 respectively.

Reaction of the aldehyde 1 with ethyl cyanoacetate gives the 2-imino-3-carbethoxydicoumarin derviative 5 by cyclization of the condensation intermediate.

Compound 1 reacts with malononitrile in the presence of ammonium acetate to yield the 2-imino-3-cyanodicoumarin derivative (6) via the addition of the proton of the hydroxy group to the cyano group followed by cyclization.

To study the reaction of 6 with active methylene compounds, it was reacted with butan-2-one and acetophenone in the presence of ammonium acetate. The reaction gives a mixture of two products, the Michael adducts 7a, b and the 2-aminopyridine derivatives 8a, b. The imino group was converted to a carbonyl group during crystallization of compounds 8a, b. This was indicated by the IR bands at 1720 and 1740 cm^{-1}.

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