CYCLIC ACYLIMINES. I. SYNTHESIS AND REACTIVITY OF ISOQUINOLINE-1,4-DIONES

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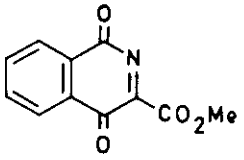
Abstract - 3-Methoxycarbonylisoquinoline-1,4-dione (1) has been prepared through elimination processes from appropriate starting materials. The quinone was trapped by cycloaddition reactions with conjugated dienes. High regioselectivity was observed. A similar approach to prepare 3-benzoylisoquinoline-1,4-dione (2) was unsuccessful.

Monoazaquinones, nitrogen heterocyclic analogues of quinones, have received only limited attention. Only 3-phenyl-[1,2] and 3-cyano-isoquinoline-1,4-dione[3] and some 2-cyanopyridine-3,6-diones[3] and their Diels-Alder adducts with symmetrical 1,3-dienes have been previously reported.

The present investigation was aimed at the preparation of 3-methoxycarbonylisoquinoline-1,4-dione (1) and 3-benzoylisoquinoline-1,4-dione (2), as well as the study of their dienophilic behaviour.



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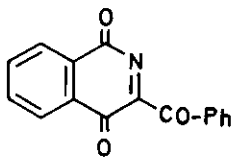

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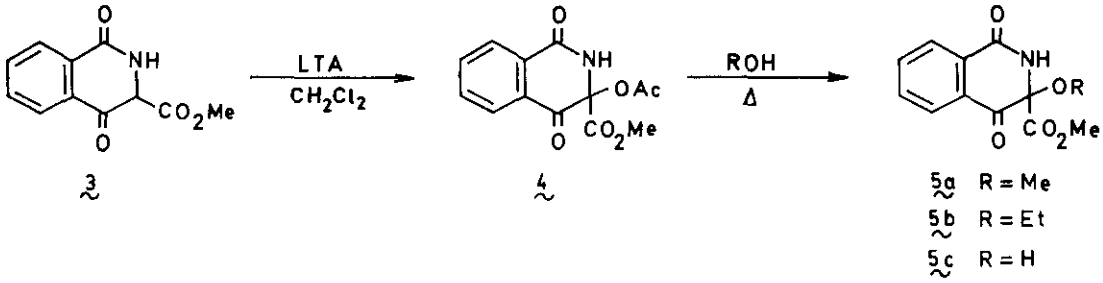
As starting materials, the corresponding 2,3-dihydro derivatives were employed. Direct oxidation of these substrates according to the general method used for the preparation of diazaquinones[4] did not work. Therefore, preparation of monoazaquinones was carried out by using the kind of procedure previously used for the obtention of 3-phenylisoquinoline-1,4-dione[1,2]. It amounts to the elimination of acetic

acid or methanol from the corresponding 3-acetoxy and 3-methoxy derivatives.

By treatment of 3 with mercuric acetate under the experimental conditions used for the preparation of 3-acetoxy-3-phenyl-2,3-dihydroisoquinoline-1,4-dione[1], starting material was recovered. Nevertheless, the reaction of 3 with lead tetraacetate in dry dichloromethane afforded the acetoxy derivative 4 in good yield. By refluxing 4 with methanol, ethanol or water, 3-methoxy- (5a), 3-ethoxy- (5b), and 3-hydroxy-3-methoxycarbonyl-2,3-dihydroisoquinoline-1,4-dione (5c) were obtained. The compound 5a was also prepared by reaction of 4 with triethylamine in methanol at room temperature. In the absence of triethylamine, the starting compound was recovered unchanged. An elimination-addition process is suggested by this result (Scheme 1).



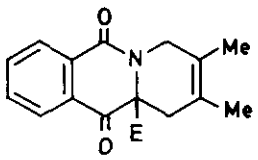
Scheme 1

Since attempts to isolate 1 by the methods reported in the literature[1,2] were unsuccessful, its generation and trapping "in situ" by cycloaddition were tried. Treatment of either 4 with triethylamine or 5a with p-toluenesulfonic acid in dry benzene afforded the monoazaquinone 1, which was trapped with 2,3-dimethylbutadiene and 1,3-cyclopentadiene giving adducts 6 and 7 respectively.

Cycloaddition of 1 with unsymmetrical dienes was highly regioselective. The reaction of 1 with 2,4-dimethyl-1,3-pentadiene afforded only adduct 8, and from the reaction with 2-methyl-1,3-pentadiene the two regioisomeric cycloadducts 9 and 10 were obtained in a 10:1 ratio.

The structural assignment of these compounds was based on the influence of the amido group on the chemical shift of adjacent protons[5]. The ^{1}H-nmr spectrum of 6 showed two doublets centered at 2.5 and 3.3 ppm (J_{gem} = 16 Hz) corresponding to the CH_2-C group and two doublets centered at 3.7 and 4.7 ppm (J_{gem} = 18 Hz) corresponding to the CH_2-N group. Therefore, structure 9 was assigned to the major adduct, in which the methyne proton appears as a multiplet centered at 4.8 ppm and the methylene protons give rise to two doublets at 2.6 and 3.3 ppm (J_{gem} = 16 Hz). On the other

hand, the minor adduct 10 showed the methyne proton at 3.4 ppm and the two doublets due to the methylene protons at 3.7 and 4.8 ppm (J_{gem} = 17 Hz).



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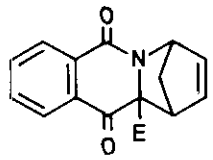

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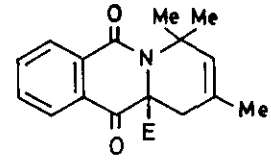

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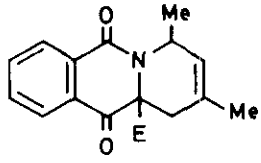
E = CO_2Me



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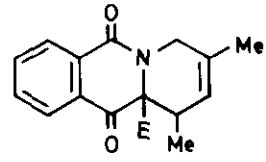

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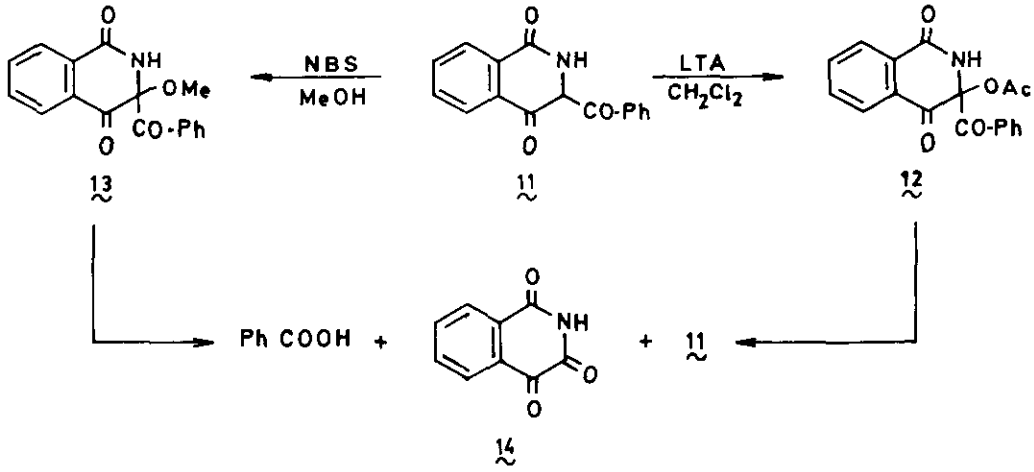
By reaction of 3-benzoyl-2,3-dihydroisoquinoline-1,4-dione (11) with lead tetraacetate the corresponding 3-acetoxy derivative (12) was obtained. Also analogue 13 was prepared by treatment of 11 with N-bromosuccinimide in methanol at -10° C. It must be pointed out that these derivatives of *monoazaquinone* 2 are much more unstable that the corresponding derivatives of 1. When allowed to stand at room temperature, these compounds undergo an spontaneous redox process leading to a mixture of the starting material (11), phthalonimide (14) and benzoic acid (Scheme 2).



13 11 12

14

Scheme 2

The same compounds were obtained when attempts were made to generate 2 from the above precursors in the presence of a diene. These results could indicate that the

precursors behave as in the absence of the diene. As an alternative interpretation, however, the monoazaquinone could be formed, but attack by a water molecule in the reaction medium is quicker that reaction with the diene. Finally the addition product thus formed undergoes a redox process.

EXPERIMENTAL

Melting points were determined in a Büchi 510 apparatus in capillary tubes and are uncorrected. The ir spectra were recorded on a Perkin-Elmer 257 spectrophotometer. The ^{1}H-nmr spectra were determined on a Varian T-60A spectrometer, chemical shifts are quoted in δ values, using TMS as internal standard. The reactions and purity of compounds were monitored by TLC, performed on silica gel plates (Merck). Compounds 3[6] and 11[7] were prepared by the methods reported in the literature.

3-Acetoxy-3-methoxycarbonyl-2,3-dihydroisoquinoline-1,4-dione (4) - To a suspension of 3 (2.2 g, 10 mmol) and magnesium oxide (0.8 g) in dry dichloromethane (40 ml) lead tetraacetate (4.4 g, 10 mmol) was added portionwise. The reaction mixture was stirred for 3 h at room temperature and filtered. The filtrate was washed with water, dried and evaporated to dryness. Recrystallization of the residue from dichloromethane/cyclohexane afforded 4 in pure form (2.2 g, 80% yield), mp 160-162°C. Ir (KBr): ν_{max} 3200, 3100 (NH), 1780, 1750, 1710, 1690 (C=O) cm^{-1}. ^{1}H-Nmr (DMSO-d_6) δ 2.17 (s, 3H, CH_3-COO), 3.73 (s, 3H, CH_3O), 7.7-8.3 (m, 4H, arom.), 9.73 (s, 1H, NH). Anal. Calc. for $C_{13}H_{11}NO_6$: C, 56.31; H, 3.97; N, 5.05. Found: C, 56,24; H,4.14; N, 5.26.

3-Methoxy-3-methoxycarbonyl-2,3-dihydroisoquinoline-1,4-dione (5a) - Compound 4 (550 mg, 2 mmol) was refluxed in methanol for 2 h. Removal of solvent and recrystallization of the residue from dichloromethane/cyclohexane afforded 5a (495 mg, 76% yield), mp 115-116°C. Ir (KBr): ν_{max} 3170, 3060 (NH), 1760, 1735, 1710, 1670 (C=O) cm^{-1}. ^{1}H-Nmr ($DCCl_3$): δ 3.38 (s, 3H, CH_3O), 3.75 (s, 3H, CH_3OCO), 7.4 (br, 1H, NH), 7.5-8.0 (m, 4H, arom.). Anal. Calc. for $C_{12}H_{11}NO_5$: C, 57.68; H, 4.64; N, 5.89. Found: C, 57.83; H, 4.45; N, 5.62.

This compound was also obtained in 30% yield by stirring a mixture of 4 (550 mg, 2 mmol) and triethylamine (0.25 ml) in dry methanol (10 ml) at room temperature for 4 h.

3-Ethoxy-3-methoxycarbonyl-2,3-dihydroisoquinoline-1,4-dione (5b) - This compound was prepared as described above for 5a using ethanol as the solvent. Yield: 65%, mp 112-114°C.(dichloromethane/cyclohexane). Ir (KBr): ν_{max} 3220, 3120 (NH), 1770, 1760,

1690, 1670 (C=O) cm^{-1}. ^{1}H-Nmr ($DCCl_3$): δ 1.23 (t, 3H, J = 7 Hz, $\underline{CH_3}$-CH_2), 3.70 (q, 2H, J = 7 Hz, $\underline{CH_2}$-CH_3), 3.80 (s, 3H, CH_3O), 7.4 (br, 1H, NH), 7.7-8.3 (m, 4H, arom) Anal. Calc. for $C_{13}H_{13}NO_5$: C, 59.32; H, 4.98; N, 5.32. Found: C, 59.55; H, 4.90; N, 5.54.

3-Hydroxy-3-methoxycarbonyl-2,3-dihydroisoquinoline-1,4-dione (5c) - This compound was obtained by the method described above, using water as the solvent. Yield: 60% mp 202-204°C. Ir (KBr): ν_{max} 3440 (OH), 3200, 3100 (NH), 1750, 1720, 1685 (C=O) cm^{-1}. ^{1}H-Nmr (DMSO-d_6): δ 3.55 (s, 3H, CH_3O), 7.3-8.0 (m, 5H, arom. + NH), 11.5 (br, 1H, OH). Anal. Calc. for $C_{11}H_9NO_5$: C, 56.18; H, 3.86; N, 5.96. Found: C,55.95; H,3.94; N, 6.17.

Acetylation of 5c with acetic anhydride in pyridine at room temperature afforded the starting compound 4 in 51% yield.

Cycloaddition reactions. General procedure - A mixture of 4 (1.5 g, 5.4 mmol), the appropriate diene (excess) and triethylamine (0.75 ml) in dry benzene (30 ml) was refluxed for 24 h. The residue obtained after removal of the solvent was chromatographed on silica gel using benzene/ethyl acetate as eluent.

2,3-Dimethyl-11a-methoxycarbonyl-1,4-dihydropyrido[1,2-b]isoquinoline-6,11-dione (6) - This compound was obtained in 15% yield, mp 144-146°C (chloroform/cyclohexane). Ir (KBr): ν_{max} 1745, 1690, 1650 (C=O) cm^{-1}. ^{1}H-Nmr ($DCCl_3$): δ 1.73 (s, 6H, CH_3-C=C), 2.53 (d, 1H, J = 16 Hz, CH_2-C), 3.30 (d, 1H, J = 16 Hz, CH_2-C), 3.70 (s, 3H, CH_3O), 3.73 (d, 1H, J = 18 Hz, CH_2-N), 4.66 (d, 1H, J = 18 Hz, CH_2-N), 7.6-8.4 (m, 4H, arom.). Anal. Calc. for $C_{17}H_{17}NO_4$: C, 68.22; H, 5.72; N, 4.68. Found: C, 68.00; H, 6.07; N, 4.44.

Adduct 6 was also prepared in 23% yield by refluxing for 24 h a mixture of 5a (0.5g, 2.0 mmol), 2,3-dimethylbutadiene (excess) and p-toluenesulfonic acid (0.1 g) in dry benzene (10 ml).

11a-Methoxycarbonyl-1,4-dihydro-1,4-methanepyrido[1,2-b]isoquinoline-6,11-dione (7) - This compound was obtained in 20% yield, mp 132-134°C (chloroform/cyclohexane) Ir (KBr): ν_{max} 1740, 1700, 1650 (C=O) cm^{-1}. ^{1}H-Nmr ($DCCl_3$): δ 1.83 (m, 2H, CH_2), 3.75 (s, 3H, CH_3O), 4.15 (m, 1H, CH-C), 5.35 (m, 1H, CH-N), 6.45 (m, 1H, CH=C), 6.75 (m, 1H, CH=C), 7.4-8.2 (m, 4H, arom.). Anal. Calc. for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.63; N, 4.94. Found: C, 67.85; H, 4.75; N, 5.16.

2,4,4-Trimethyl-11a-methoxycarbonyl-1,4-dihydropyrido[1,2-b]isoquinoline-6,11-dione (8) - This compound was obtained in 6% yield, mp 136-137°C (chloroform/cyclohexane). Ir (KBr): ν_{max} 1735, 1685, 1660 (C=O) cm^{-1}. ^{1}H-Nmr ($DCCl_3$): δ 1.60 and 1.67

(2s, 6H, $2CH_3$), 1.87 (m, 3H, CH_3-C=C), 2.42 (d, 1H, J = 17 Hz, CH_2-C), 3.40 (d, 1H, J = 17 Hz, CH_2-C), 3.65 (s, 3H, CH_3O), 5.25 (m, 1H, CH=C), 7.4-8.5 (m, 4H, arom.). Anal. Calc. for $C_{18}H_{19}NO_4$: C, 68.93; H, 6.11; N, 4.47. Found: C, 68.69; H, 6.40; N, 4.59.

2,4-Dimethyl-11a-methoxycarbonyl-1,4-dihydropyrido[1,2-b]isoquinoline-6,11-dione (9) - This compound was obtained in 12% yield, mp 124-126°C (chloroform/cyclohexane). Ir (KBr): ν_{max} 1730, 1685, 1660 (C=O) cm^{-1}. ^{1}H-Nmr ($DCCl_3$): δ 1.38 (d, 3H, J = 7 Hz, CH_3-C-N), 1.8 (s, 3H, CH_3C=C), 2.60 (d, 1H, J = 16 Hz, CH_2-C), 3.33 (d, 1H, J = 16 Hz, CH_2-C), 3.60 (s, 3H, CH_3O), 4.85 (m, 1H, CH-N), 5.55 (m, 1H, CH=C), 7.4-8.4 (m, 4H, arom.). Anal. Calc. for $C_{17}H_{17}NO_4$: C, 68.22; H, 5.72; N, 4.68. Found: C, 68.07; H, 5.88; N, 4.78.

1,3-Dimethyl-11a-methoxycarbonyl-1,4-dihydropyrido[1,2-b]isoquinoline-6,11-dione (10) - This compound was obtained in 1% yield, mp 93-95°C (n-pentane). Ir (KBr): ν_{max} 1730, 1680, 1650 (C=O) cm^{-1}. ^{1}H-Nmr ($DCCl_3$): δ 0.87 (d, 3H, J = 7 Hz, CH_3-C-C), 1.73 (s, 3H, CH_3-C=C), 3.68 (s, 3H, CH_3O), 3.4-4.1 (m, 2H, CH-C and CH_2-N), 4.77 (d, 1H, J = 17 Hz, CH_2-N equatorial), 5,67 (m, 1H, CH=C), 7.4-8.5 (m, 4H, arom.). Anal. Calc. for $C_{17}H_{17}NO_4$: C, 68.22; H, 5.72; N, 4.68. Found: C, 68.32; H, 5.84; N, 4.68.

3-Acetoxy-3-benzoyl-2,3-dihydroisoquinoline-1,4-dione (12) - This compound was prepared by using the method described for the preparation of 4, starting from the corresponding dihydro derivative 11. Yield: 40%, mp 180-181°C (chloroform/cyclohexane). Ir (KBr): ν_{max} 3195, 3090 (NH), 1740, 1710 (C=O) cm^{-1}. ^{1}H-Nmr (DMSO-d_6): δ 2.20 (s, 3H, CH_3-COO), 7.4-8.2 (m, 9H, arom.), 11.6 (s, 1H, NH). This compound proved to be unstable and on standing undergoes a spontaneous transformation leading to starting material (11), phthalonimide (14), and benzoic acid.

3-Benzoyl-3-methoxy-2,3-dihydroisoquinoline-1,4-dione (13) - To a cold suspension (-10°C) of 11 (4.0 g, 15 mmol) in dry methanol (150 ml), freshly recrystallized N-bromosuccinimide (2.7 g, 15 mmol) was added. After stirring for 15 minutes, the precipitate was filtered off and washed with cold methanol. Recrystallization from methanol afforded 13 in pure form (3.5 g, 78% yield), mp 184-186°C. Ir (KBr): ν_{max} 3190, 3090 (NH), 1680 (C=O) cm^{-1}. ^{1}H-Nmr (DMSO-d_6): δ 3.40 (s, 3H, CH_3O), 7.0-8.2 (m, 9H, arom.), 9.37 (s, 1H, NH). This compound is unstable and oxidizes spontaneously on standing to phthalonimide (14), 11, and benzoic acid.

Attempts for the Generation of 2 in the Presence of 2,3-Dimethylbutadiene - To a mixture of 12 (323 mg, 1.0 mmol) and triethylamine (0.14 ml) or to a mixture of 13

(295 mg, 1.0 mmol) and p-toluenesulfonic acid (50 mg) in dry benzene (15 ml), an excess amount of 2,3-dimethylbutadiene was added. The reaction mixture was refluxed for 8 h and the solvent was then evaporated to dryness. Chromatography of the residue on silica gel using benzene-ethyl acetate (4:1) as eluent afforded 40 % of 3-benzoyl-2,3-dihydroisoquinoline-1,4-dione (11), 24% of phthalonimide (14), and benzoic acid.

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