DIRECT ACCESS TO 4-SUBSTITUTED 3-ISOCHROMANONES BY THE pH CONTROLLED ADDITION OF ALDEHYDES

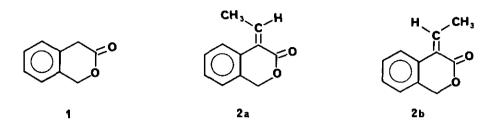
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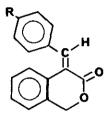
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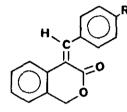
<u>Abstract</u>-Aldehydes condense at position 4 of 3-isochromanone in the presence of a base, in competition with the ring opening of the lactone. By control of the pH, the new syn and anti 4-ethylidene and benzylidene derivatives are obtained with yields of 30 and 28%. Due to the strong interaction of the olefinic proton with the carbonyl group of the lactone, in particular in the case of the stilbene structures prepared through reaction with a benzaldehyde, these syn and anti isomers are easily resolved by chromatography and characterized. The 4-methylene 3-isochromanone obtained through addition of formaldehyde is not stable and polymerizes readily to a mixture of polymers.

During the course of studies on the reactivity of pyrano-naphthoquinones of the fusarubine type and more particularly in relationships with the possible origin of nectriafurone<sup>1</sup>, we were brought to carry out reactions on 3-isochromanone chosen as a model (1,4-dihydro-3H-2-benzopyran-3-one <u>1</u>), a commercially available compound (Aldrich-Europe). Astonishingly enough, the condensation of aldehydes on the activated methylene group at position 4 of 3-isochromanone is not reported and the pH controlled addition affords the expected 4-ene substituted derivatives with reasonable yields, so that we wish to describe the results of our experiments. By using an excess of acetaldehyde in ethanol and the slow addition of a KOH solution under control of the pH, a 30% yield of a l:l mixture of the two syn and anti isomers <u>2a</u> and <u>2b</u> (4-ethylidene 3-isochromanones) is observed. These products are easily resolved by chromatography and characterized, in particular in <sup>1</sup>H NMR, because of the interaction of the olefinic proton with the carbonyl in <u>2a</u>. With benzaldehyde, the two stilbene lactones <u>3a</u> and <u>3b</u> (syn and anti 4-benzylidene

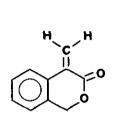
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3a R = H5a R = OH 3b R = H5b R = OH



3-isochromanones) are obtained in the ratio of 1:1 with an overall yield of 28%. These lactones 2a, 2b, 3a, 3b, appear to be relatively stable products as shown by control TLC carried out on solutions kept for several days at 0°C and in absence of light.

The addition of formaldehyde on <u>1</u> leads to the less stable 4-methylene 3-isochromanone <u>4</u> with a 20% yield.Analyses have to be carried out rapidly on this substance as it polymerizes readily into a dimer according to MS determination.However,the NMR spectra can not be interpreted any more and suggest the presence of a mixture of polymers.

In the case of the 4-ethylidene isochromanones 2a and 2b, attempts were made to use triethylamine or LDA in THF or  $Et_20$  but the reactions were abandoned after repetitions with different concentrations because of the lower yields which were observed (8 and 6% respectively). It seems that the strength of the base is a determinant factor in this reaction, hence an unavoidable competition with the hydrolysis of the lactone.

The reaction of 3-isochromanone was carried out with p-hydroxy benzaldehyde, the

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resulting syn and anti 4-(p-hydroxy benzylidene 3-isochromanones 5a and 5b representing potential estrogens, in particular the syn (transoid) stilbene structure  $5b^2$ . These substances were obtained with an overall yield of 8%. That the 4-ene lactones are present in the media when the starting 3-isochromanone <u>1</u> has nearly completely disappeared means of course that they are more stable.Nevertheless, the hydrolysis of the lactone by the base remains the principal reaction, as 70 to 80% of the starting material is lost. This competitive addition of the aldehyde at position 4, previous to the lactone opening is, however, of particular interest because of its great simplicity and because it gives a general access to a family of heterocyclic compounds which could not be synthesized so easily by other methods.

In relationships with the isofuranic structure of nectriafurone<sup>1</sup>, attempts were made to epoxidize the ethylidene isochromanones 2a and 2b, in view of their rearrangement into isofuranic compounds<sup>3-5</sup>, but assays carried out with m-chloro perbenzoic acid failed, very likely due to the conjugation of the yet exocyclic double bond in these products.

## EXPERIMENTAL

Mps have been determined with a Kofler apparatus under the microscope and are corrected.Mass spectrometry has been carried out on an AEI MS 50 apparatus and <sup>1</sup>H NMR on a Bruker 200 MHz spectrometer,  $\text{CDCl}_3$ , zero TMS, $\delta$  ppm, UV spectra on a Lambda-5 automatic recorder Perkin-Elmer.

Syn and anti 4-ethylidene 3-isochromanones 2a and 2b: in a typical experiment, 100 mg (0.67 mM) of 3-isochromanone <u>1</u> dissolved in 8 ml ethanol were used, and 300 mg acetaldehyde (10 mM) added. A solution of 100 mg KOH in 3 ml ethanol was then slowly added under stirring, at room temperature. The drop by drop addition of the base was stopped when the pH reached 9 and continued when under 8. The reaction was followed by  $SiO_2$  TLC on Schleicher-Schull films, development with hexane-ethyl acetate (4:1), UV observation (Desaga lamp) at 254 nm. The addition of the base was definitly stopped when only a trace of the starting material was noticed from the TLC (Rf 0.45). The reaction mixture was then transferred into a separating funnel, 2 volumes of ether and 3 volumes of water were added and the organic layer immediately decanted without shaking, quickly washed with water, dried over  $Na_2SO_4$  and submitted to preparative TLC in the same conditions (SiO<sub>2</sub> plates, 1 mm thickness) for

isolation. The substances were recovered from the scrapped SiO, by ether, filtration on a cotton plug and evaporation. By using this method, a 30% yield of a 1:1 ratio of the isomers 2a and 2b could be obtained (35 mg of the mixture). 2a : Rf. 0. 60, mp. 41-45°C,  $\lambda$  max. ether, nm, 225 ( $\xi$  7. 5x10<sup>3</sup>), 256 ( $\xi$  7. 7x  $10^3$ ), e. 1. MS, m/z 174, (M<sup>+</sup>), Anal. calc. for  $C_{11}H_{10}O_2$  : C, 75. 84; H, 5. 79; found: C, 75. 94; H, 5. 82. <sup>1</sup>H NMR, 7. 20 (olefinic proton, 1H, q, 8 Hz), 2. 20 (CH<sub>2</sub>, 3H, d, 8 Hz), 5. 30 (OCH<sub>2</sub>, 2H, s), 7. 3-7. 5 (aromatic protons, 4H, m). <u>2b</u> : Rf O. 70, oil, anal. calc. for  $C_{11}H_{10}O_2$  : C, 75. 84; H, 5. 79; found, C, 75. 88,H, 5. 82; similar properties in MS and NMR, but olefinic proton at § 6. 85 (q, 8 Hz), and CH<sub>2</sub> signal displaced at  $\delta$  2. 95. Syn and anti 4-benzylidene 3-isochromanones 3a and 3b : these products were obtained under the same conditions as for substances 2a and 2b, starting with benzaldehyde and 1, in the ratio 1:1 and an overall yield of 28%. 3a : Rf. 0. 60, mp; 125-129°C,  $\lambda$  max. ether, nm, 227 ( $\xi$  1.3x10<sup>4</sup>), 315 ( $\xi$  8.8x 10<sup>3</sup>), MS, m/z 236 (M<sup>+</sup>), anal. calc. for  $C_{16}H_{12}O_{2}$  : C, 81. 34; H, 5. 12; found: C, 81, 28; H, 5.09; <sup>1</sup>H NMR, olefinic proton for the syn stilbene  $^{6}$  at  $\pmb{\delta}$  7.90, (1H, s), 7. 3-7. 6 (aromatic protons, 9H), 5.38 (OCH<sub>2</sub>, 2H, s). <u>3b</u> : Rf. 0. 40, mp. 56-60°C; anal. calc. for C<sub>16</sub>H<sub>12</sub>O<sub>2</sub> : C,81. 34; H, 5. 12; found: 81. 30; H, 5. 10; similar properties in MS and <sup>1</sup>H NMR, except for the olefinic proton at  $\delta$  7. 30 (lH, s), corresponding to the anti form. 4-methylene 3-isochromanone 4 : this substance is formed by condensation of  $\underline{1}$ 

with formaldehyde with a 20% yield.

<u>4</u>: Rf. 0. 55 in hexane-ethyl acetate (4:1), oil, MS, m/z 160 (M<sup>+</sup>); anal. calc. for  $C_{10}H_8O_2$ : C, 74. 99; H, 5. 03; found: C, 74. 82; H, 5. 15; <sup>1</sup>H NMR, methylene protons at  $\delta$  6. 65 (1H, s), and 6. 25 (1H, s), 5. 40 (OCH<sub>2</sub>, 2H, s), this substance polymerizes readily (20 h at 0°C) into a white product mp. 206-210°C, Rf. 0. 05, MS, M<sup>+</sup> at m/z 320 corresponding to a dimer. However, the NMR spectrum can not be interpreted any more and suggests the presence of a mixture of higher polymers.

<u>Syn and anti 4-(p-hydroxybenzylidene) 3-isochromanones 5a and 5b</u> : these substances were prepared by reaction of <u>1</u> with p-hydroxybenzaldehyde as described for <u>2a</u> and <u>2b</u>, (15 mM aldehyde for 1 mM of starting material). In this case, due to the presence of the phenolic OH group, acidification with dilute HCl was necessary after the reaction and previous to extraction. The mixture of the isomers

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5a and 5b was separated by preparative SiO<sub>2</sub> TLC, development with hexane-ethyl acetate (2:3), overall yield 8%. 5a: amorphous product, Rf. 0. 35, MS, m/z 252, M<sup>+</sup>; anal. calc. for  $C_{16}H_{12}O_3$ : C,76. 18; H, 4. 80; found: C, 76. 08; H, 4. 90; <sup>1</sup>H NMR, olefinic proton (1H, s) at 8 7. 95. 5b: amorphous product, anal. calc. for  $C_{16}H_{12}O_3$ : C,76. 18; H, 4. 80; found, C, 76. 11; H, 4. 88; MS and <sup>1</sup>H NMR 1d. 5a, but olefinic proton (1H, s) at  $\delta$  7. 30. ACKNOWLEDGEMENTS Thanks are due to Drs B. C. Das and C. Girard for mass spectrometric determinations and to the Service de Microanalyses du CNRS at Gif sur Yvette. REFERENCES 1. D. Parisot, M. Devys, J. P. Férézou, and M. Barbier, Phytochemistry, 1983, 22, 1301. 2. U. V. Solmssen, Chem. Rev. , 1945, 37, 481. 3. J. G. Smith, and P. W. Dibble, Tetrahedron, 1984, 40, 1667. 4. J. G. Smith, and G. Kruger, J. Org. Chem. ,1985, 50, 5759. 5. W. Friedrichsen, B. M. König, K. Hildebrandt, and T. Debaermaeker, Hetero-<u>cycles</u>, 1986, 24, 297. 6. C. N. Banwell, and N. Sheppard, Mol. Phys. , 1960, 3, 251.

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