MICHEAL CONDENSATION OF ETHYL-3(H)-OXONAPHTHO (2,1-b)PYRAN-2-CARBOXYLATE WITH KETONES

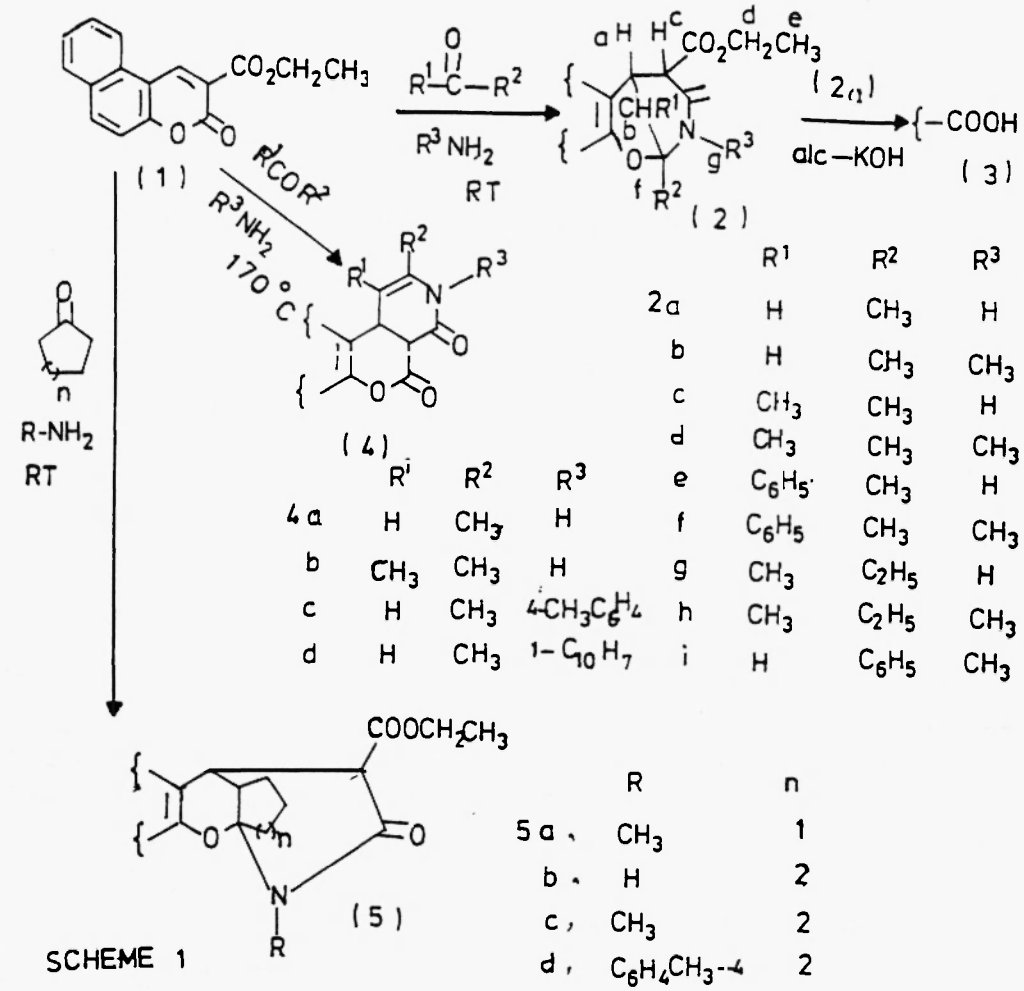
M.R. Selim, A.M. El-Agrody, A.H. Bedair and F.M. Aly
Department of Chemistry, Faculty of Science, Al-Azhar University, Nasr City, Cairo, Egypt

Abstract: Condensation of ethyl 3(H)-oxonaphtho (2,1-b) pyran-2-carboxylate (1) with ketones in the presence of ammonium acetate or amines at room temperature gave the corresponding naphthoxazocine carboxylates (2) via a Micheal addition. While condensation of (1) with ketones in a sealed tube at 170°C in the presence of ammonium acetate or aromatic amines gave 1,3-disubstituted-2-methyl-4a, 12b-dihydro-4H [1H] naphtho (2,1-b) pyrano [3,4-c] pyridine-4,5 (3H)-dione (4). The structure assigned are supported by ^{1}H-NMR, IR spectra and microanalyses.

Results and Discussion

In view of the biological activity shown by certain oxazocine and pyridine derivatives (1-5) and in continouation of our previous work (6-10), it seemed of interest to synthesis some noval derivatives of naphthoxazocine carboxylates and naphthopyranopyridinediones via the interaction of ethyl -3(H) oxonaphtho (2,1-b) pyran-2-carboxylate 1 with different ketones.

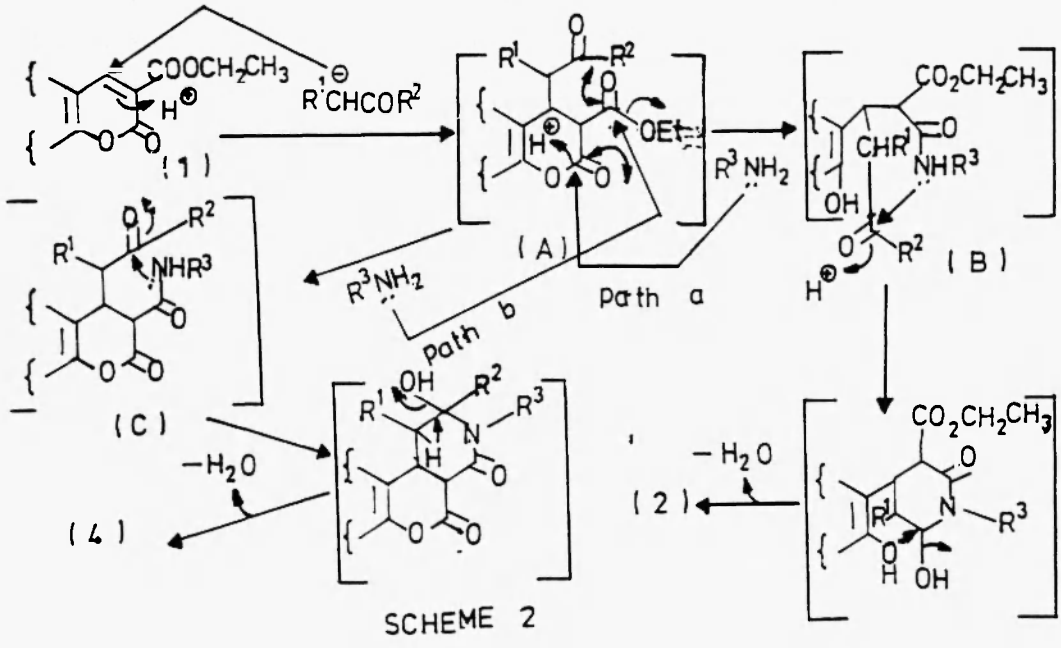
Treatment of 1 with acetone. methyl ethylketone, methylbenzylketone, diethyl ketone or acetophenone in the presence of ammonium acetate or methylamine at room temperature yielded ethyl 3,13 (dialkyl/aryl)-4-oxo-2,6-methano-2-alky/aryl-3,4,5,6-tetrahydro-2H-naphtho (2,1-g)-1,3-oxazocine-5-carboxylates 2a-i (Scheme 1). The IR spectrum of 2a showed ν-lactam at 1650, CO of ester at 1730, aliphatic CH at (2940-3045) and NH at 3260 cm^{-1}. ^{1}H-NMR spectrum of 2a showed a triplet at δ1.3 for methyl protons (e), a singlet at 1.8 for methyl protons (f), a quartet at 2.4 for methylene protons (b), AB-system (Jgem = 15 Hz), a multiplet at 3.45 and a doublet at 3.9, Jac = 7 Hz for the methine protons a & c, a quartet at 4.3 for methylene protons (d), J_{de} and J_{ed} = 6 Hz respectively, a broad band at 6.8



	R^1	R^2	R^3
2a	H	CH_3	H
b	H	CH_3	CH_3
c	CH_3	CH_3	H
d	CH_3	CH_3	CH_3
e	C_6H_5	CH_3	H
f	C_6H_5	CH_3	CH_3
g	CH_3	C_2H_5	H
h	CH_3	C_2H_5	CH_3
i	H	C_6H_5	CH_3

	R^1	R^2	R^3
4a	H	CH_3	H
b	CH_3	CH_3	H
c	H	CH_3	$4\text{-}CH_3C_6H_4$
d	H	CH_3	$1\text{-}C_{10}H_7$

	R	n
5a	CH_3	1
b	H	2
c	CH_3	2
d	$C_6H_4CH_3\text{-}4$	2



for the imide proton (g) obscured by D_2O, and a multiplet at 6.8-8 ppm for the aromatic protons.

The ester derivatives of 2a was hydrolyised with alcoholic potassium hydroxide giving 3-methyl-4-oxo-2,6-methano-2-methyl-3,4,5,6-tetrahydro-2H-naphtho (2,1-g)1,3-oxazo-cine-5-carboxylic acid 3.

Condensation of 1 with acetone or ethyl methyl ketone in the presence of ammonium acetate, p-toluidine & 1-naphthylamine under fuision at 170°C in a sealed tube gave 1,3-disubstituted-2-methyl-4a, 12b-dihydro (4H) [1] naphtho (2,1-b) pyrano-[2,4c] pyridine-4.5 (3H)-dione (4a-d). IR of 4a showed ν-(lactone-saturated) at 1640, (lactam) at 1610 and NH at 3200 cm^{-1}. Finally condensation of 1a with cyclopentanone and cyclohexanone at room temperature in the presence of ammonium acetate, methylamine and p-toluidine leads to the formation of 5,6-benzo-2-methylimino-2,3-trimethylene chroman-4α-carboxyacetic acid lactam 5a and ethyl 12-oxo-1,2,3,4,9,9a hexahydro-4a, 9-alkyl/aryliminoethano-4aH-7,8-benzoxanthene-11-carboxylate (5b-d) respec- tively, the IR spectrum of 5a showed ν(δ-lactam) at 1660, (CO) (ester) at 1740 and aliphatic CH cyclic at 2895-3085 cm^{-1}. The IR of 5b showed ν(δ-lactam) at 1640, CO(ester) at 1700, aliphatic CH cyclic at 2830-3080 and NH at 3180 cm^{-1}.

The reaction mechanism of the prepared compounds can be rationalised as a Micheal addition of ketone to the C_1-C_2 olefmic bond in pyran nucleus to give the intermediate (A) Scheme 2, fission of the heterocyclic ring with ammonia or with amine (path a) to give (B) which under subsequent intramolecular nucleo cyclization with elimination of water molecule gave 2. However, in (path b), the pyran nucleus remains intacted, while the carboxamide (C) cyclized followed by subsequent elimination of water molecule to give 4.

Experimental

All melting points are uncorrected, IR spectrum were recorded on a pye-unicam sp 1200, ^{1}H-NMR spectrum were recorded on BM 360 n.m.r instrument using TMS as an internal standard.

Condensation of 2-substituted-3(H)-oxonaphtho(2,1-b)pyran (1) with ketones

A- At room temperature

A solution of (1a) (0.01 mole), ketone (0.01 mole) and ammonium acetate or amine (0.025 mole) in ethanol was kept at room temperature for 3 days, the solvent was

Table 1 : Characterization data of the various prepared compounds

Comp.	M.p. °C	Formula Mol.wt	Analysis Found /Required C	H	N
2a	208	$C_{19}H_{19}NO_4$	70.40	5.60	4.20
		325	70.15	5.85	4.31
b	180	$C_{20}H_{21}NO_4$	70.30	6.30	4.40
		339	70.80	6.19	4.13
c	188	$C_{20}H_{21}NO_4$	70.30	6.30	4.40
		339	70.80	6.19	4.13
d	215	$C_{21}H_{23}NO_4$	71.60	6.80	4.10
		353	71.39	6.52	3.97
e	157	$C_{25}H_{23}NO_4$	75.00	5.80	3.60
		401	74.81	6.74	3.49
f	232	$C_{26}H_{25}NO_4$	75.20	6.10	3.50
		415	75.18	6.02	3.37
g	203	$C_{21}H_{23}NO_4$	71.40	6.60	4.00
		353	71.39	6.52	3.97
h	220	$C_{22}H_{25}NO_4$	72.10	6.90	4.00
		367	71.93	6.81	3.81
i	230	$C_{25}H_{23}NO_4$	75.00	5.90	3.60
		401	74.81	5.74	3.49
3	195	$C_{19}H_{17}NO_4$	70.30	5.10	4.30
		323	70.58	5.26	4.33
4a	260	$C_{17}H_{13}NO_3$	73.20	4.80	5.00
		279	73.12	4.66	5.02
b	265	$C_{18}H_{15}NO_3$	73.50	5.30	4.60
		293	73.72	5.12	4.78
c	214	$C_{24}H_{19}NO_3$	77.80	5.30	3.50
		369	78.05	5.15	3.79
d	260	$C_{27}H_{19}NO_3$	79.70	4.60	3.20
		405	80.00	4.89	3.40
5a	192	$C_{22}H_{23}NO_4$	72.10	6.20	3.50
		365	72.33	6.30	3.84
b	325	$C_{22}H_{23}NO_4$	72.50	6.30	3.90
		365	72.33	6.30	3.84
c	208	$C_{23}H_{25}NO_4$	72.50	6.20	3.40
		379	72.82	6.60	3.69
d	204	$C_{29}H_{29}NO_4$	76.60	6.10	3.20
		455	76.48	6.37	3.08

evaporated. stirred with conc. HCl (20 ml), then with H_2O and finally allowed to stand for several hours. The products were Crystallized from suitable solvents to give give 2. and 5, Table 1 yield 40-80%.

B- At 170°C

A mixture of 1 (0.01 mole), ketone (0.01 mole) and ammonium acetate or amine (p-toluidine or 1-naphthylamine) (0.025 mole) in a sealed tube was heated at 170°C for 6 hrs. The residue was stirred with conc. HCl (20 ml, washed with H_2O and crystallized from a proper solvent to give 4 Table (1), yield 40-70% respectively.

Synthesis of 3-methyl-4-oxo-2,6-methano-2-methyl-3,4,5,6-tetrahydro-2H-naphtho (2,1-g) 1,3-oxazocine-5-carboxylic acid (3)

A mixture of compound 2a, (0.01 mole), potassium hydroxide 0.5 gm in ethanol (30 ml) was heated under reflux for 3 hours, cool it down to give a solid which was crystallized from benzene to give 3 in 65% yield, Table 1.

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Received August 5, 1996