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SYNTHESIS OF 3-AROYLMETHYLENE-1,6,7,11b-TETRAHYDRO-2H-PYRAZINO-[2,1-*a*]ISOQUINOLIN-4-ONES

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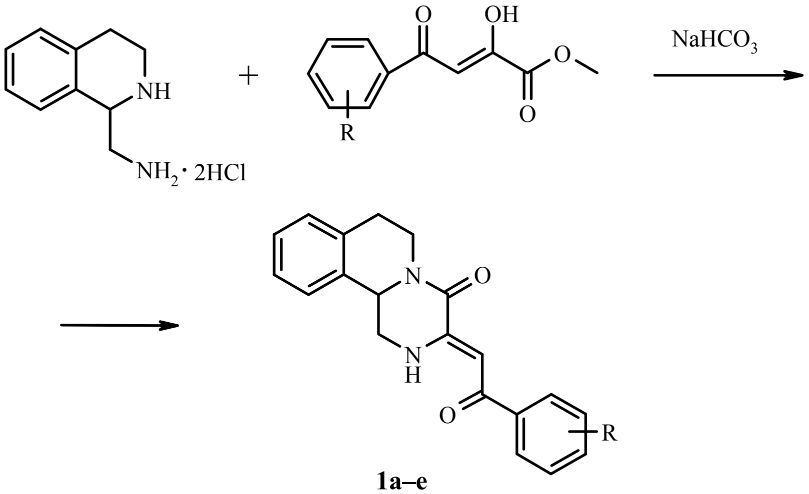
The reaction of substituted methyl aroylpyruvates with 1-aminomethyl-1,2,3,4-tetrahydroisoquinoline dihydrochloride in the presence of AcOH gives 3-aroylmethylene-1,6,7,11b-tetrahydro-2H-pyrazino[2,1-a]isoquinolin-4-ones whose structures have been confirmed by IR, ^1H NMR, and mass spectrometry.

Keywords: 1-aminomethyl-1,2,3,4-tetrahydroisoquinoline, 3-aroylmethylene-1,6,7,11b-tetrahydro-2H-pyrazino[2,1-*a*]isoquinolin-4-ones, substituted aroylpyruvate esters.

The reaction of methyl acylpyruvates with ethylenediamine gives 3-acylmethylenepiperazin-2-ones which show marked anti-inflammatory activity [1, 2]. With the aim of synthesizing novel biologically active compounds we now report a study of the reaction of methyl aroylpyruvates with 1-aminomethyl-1,2,3,4-tetrahydroisoquinoline.

It was found that refluxing equimolar amounts of the indicated reagents in a mixture of ethanol and water in the presence of AcOH gives 3-aroylmethylene-1,6,7,11b-tetrahydro-2H-pyrazino[2,1-a]isoquinolin-4-ones:



1a–e

1 a R = H, **b** R = 4-F, **c** R = 4-Me, **d** R = 3-OMe, **e** R = 3,4-$(OMe)_2$

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TABLE 1. Parameters for the 3-Aroylmethylene-1,6,7,11b-tetrahydro-2H-pyrazino[2,1-*a*]isoquinolin-4-ones **1a-e**

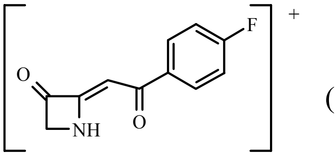
Compound	Empirical formula	Found, % / Calculated, % C	N	H	mp, °C (ethanol)	Yield, %
1a	$C_{20}H_{18}N_2O_2$	75.42 75.45	8.75 8.80	5.60 5.70	200-202	67.0
1b	$C_{20}H_{17}FN_2O_2$	71.42 71.41	8.34 8.33	5.15 5.10	212-213	75.4
1c	$C_{21}H_{20}N_2O_2$	75.83 75.88	8.39 8.43	6.06 6.07	204-206	78.2
1d	$C_{21}H_{20}N_2O_3$	72.40 72.39	8.04 8.04	5.76 5.79	160-162	38.4
1e	$C_{22}H_{22}N_2O_4$	69.79 69.82	7.41 7.40	5.87 5.86	170-172	84.8

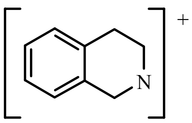
The compounds obtained are colorless or yellow crystalline materials, soluble in conventional organic solvents (Table 1).

The IR spectra of compounds **1a-e** (Table 2) shown absorption bands for the stretching vibrations of the lactam carbonyl group at 1648-1668, the ketonic carbonyl group of the phenacylidene residue at 1608-1612, and the N–H bond at 3185-3247 cm^{-1}.

The ^1H NMR spectra of compounds **1a-e** (Table 2) show signals for the methylene group protons in positions 1, 6, and 7 at 2.87-2.90 (2H), 2.98-2.99 (1H), 4.02-4.04 (1H), 4.65-4.69 (1H), and 5.09-5.12 ppm (1H), a signal for the 11b methine proton at 3.24-3.28 ppm, a singlet for the aroylmethylene residue proton at 6.55-6.59 ppm, a group of aromatic proton signals at 7.00-7.94 ppm, and a signal for the NH proton at position 2 at 10.69-10.85 ppm as well as a signal for the methyl group protons at 2.39 ppm (for compound **1c**) or the methoxy group at 3.82 ppm (for compounds **1d,e**).

The mass spectrum of compound **1b** shows peaks at *m/z* (*I*, %): 336 $[M]^+$ (13),

205 

(5), 132 

(100),

123 $[FC_6H_4CO]^+$ (12), and 95 $[FC_6H_4]^+$ (12) which are in complete agreement with this structure.

EXPERIMENTAL

IR spectra were recorded on UR-20 and Specord-85 instruments as a suspension in vaseline oil. ^1H NMR spectra were obtained on a Bruker DRX 500 (500 MHz) instrument using DMSO-d_6 and with TMS internal standard. The mass spectrum of compound **1b** was taken on an MX-1320 spectrometer with an ionization energy of 70 eV.

3-Aroylmethylene-1,6,7,11b-tetrahydro-2H-pyrazino[2,1-a]isoquinolin-4-ones 1a-e (General Method). A solution of $NaHCO_3$ (10 mmol) in water (5 ml) was added to a solution of the 1-aminomethyl-1,2,3,4-tetrahydroisoquinoline (5 mmol) in 96% ethanol (5 ml) and slightly heated until the evolution of gas

TABLE 2. Spectroscopic Characteristics for Compounds **1a-e**

Compound	IR spectrum, ν, cm^{-1}			^{1}H NMR spectrum, δ, ppm (*J*, Hz)					
	CON	C=O	NH	CH$_2$	C$_{(11b)}$H, t	CH=, s	Ar	NH, d	Others protons
1a	1664	1610	3238	2.87 (2H, m); 2.98 (1H, m); 4.04 (1H, m); 4.64 (1H, q, ^2J = 11. 83, ^3J = 3.46); 5.11 (1H, q, ^2J = 12.10, ^3J = 3.85)	3.27 (^2J = 12.81)	6.59	7.27 (4H, m); 7.52 (3H, m); 7.89 (2H, m)	10.85 (^3J = 4.93)	
1b	1658	1610	3203	2.89 (2H, m); 2.98 (1H, m); 4.02 (1H, m); 4.68 (1H, q, ^2J = 12.48, ^3J = 3.87); 5.09 (1H, q, ^2J = 12.05, ^3J = 3.61)	3.26 (^2J = 12.67)	6.55	7.28 (6H, m); 7.96 (2H, m)	10.81 (^3J = 4.60)	
1c	1668	1610	3241	2.89 (2H, m); 2.98 (1H, m); 4.02 (1H, m); 4.68 (1H, q, ^2J = 12.44, ^3J = 3.33); 5.09 (1H, q, ^2J = 11.98, ^3J = 3.44)	3.25 (^2J = 12.60)	6.57	7.28 (6H, m); 7.80 (2H, d, ^3J = 7.86)	10.78 (^3J = 4.69)	2.39 (3H, s, CH$_3$)
1d	1648	1608	3185	2.90 (2H, m); 2.99 (1H, m); 4.04 (1H, d, ^2J = 13.03); 4.67 (1H, d, ^2J = 12.32); 5.10 (1H, d, ^2J = 11.90)	3.27 (^2J = 12.61)	6.56	7.08 (1H, d, ^3J = 7.94); 7.27 (3H, m); 7.33 (1H, d, ^3J =7 .30); 7.38 (2H, m); 7.47 (1H, d, ^3J = 7.55)	10.81 (^3J = 4.31)	3.82 (3H, s, OCH$_3$)
1e	1652	1612	3247	2.89 (2H, m); 2.98 (1H, m); 4.02 (1H, m); 4.68 (1H, m); 5.08 (1H, d, ^2J = 11.93, ^3J = 3.77)	3.25 (^2J = 12.54)	6.57	7.01 (1H, d, ^3J = 8.38); 7.27 (3H, m); 7.33 (1H, d, ^3J =7 .31); 7.44 (1H, s); 7.52 (1H, d, ^3J = 8.37)	10.69 (^3J = 5.05)	3.83 (6H, s, 3,4-(OCH$_3$)$_2$)

ceased. A solution of the methyl acylpyruvate (5 mmol) in 96% ethanol (5 ml) and glacial AcOH (2.5 ml) was then added and refluxed for 1 h. After cooling, the precipitated solid was filtered off and recrystallized from ethanol.

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