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ALIPHATIC ALDEHYDES IN THE SYNTHESIS OF CONDENSED 4-ALKYL(CYCLOALKYL)-2-AMINO-3-CYANO-4H-PYRANS

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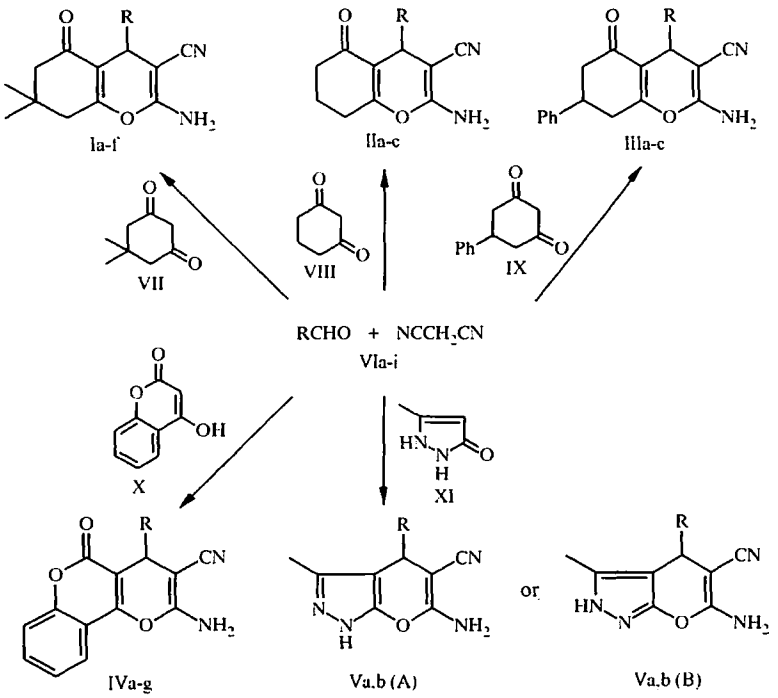
Substituted 4-alkyl(cycloalkyl)-2-amino-3-cyano-4H-pyrans have been obtained from the reaction of aliphatic aldehydes with malononitrile and some other CH acids in the presence of N-methylmorpholine.

Recently the first report appeared on the synthesis of 4-alkyl-2-amino-4H-tetrahydrobenzopyrans from the reaction of unsaturated nitriles with cyclohexan-1,3-dione [1]. The unsaturated nitriles required for this route are difficult to prepare. We had previously synthesized the corresponding 4-alkyl-2-amino-3-cyanobenzopyrans in



I, II, VI a R = *i*-Bu, b R = $PhCH_2$, c R = cyclohex-3-enyl, d R = Pr, e R = cyclohexyl, f R = Me, g R = *i*-Pr, h R = heptyl, i R = $Ph(CH_2)_2$; III a R = *i*-Pr, b R = $PhCH_2$, c R = cyclohexyl; IV a R = *i*-Pr, b R = $PhCH_2$, c R = cyclohexyl, d R = heptyl, e R = cyclohex-3-enyl, f R = *i*-Bu, g R = $Ph(CH_2)_2$; V a R = *i*-Pr, b R = *i*-Bu.

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quantitative yields by condensation of dimedone, malononitrile, and propionaldehyde or isobutyraldehyde [2]. In continuation of this study we have developed a suitable method for preparation of 4-alkyl(cycloalkyl)-2-amino-3-cyano-4-pyrans I-V, condensed with various carbo- and heterocyclic compounds.

Reaction of the aliphatic aldehydes VIa-i with malononitrile and CH acids — dimedone, cyclohexan-1,3-dione, 5-phenyl-1,3-cyclohexandione, 4-hydroxycoumarin and 3-methyl-3-pyrazolin-5-one (VII-XI respectively) – at 20°C in ethanol in the presence of an equimolar quantity of N-methylmorpholine leads to the formation of the corresponding derivatives of 4H-pyrans I-V. It was not possible at this stage of the investigation to reach and unambiguous conclusion about the structure of the pyrazolopyrans (VA or VB). The characteristics of the compounds synthesized are given in Tables 1 and 2.

TABLE 1. Characteristics of the Synthesized Compounds I-V

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
Ia	$C_{16}H_{22}N_2O_2$	69.80 / 70.04	8.19 / 8.08	9.91 / 10.21	156-157	78
Ib	$C_{19}H_{20}N_2O_2$	74.16 / 74.00	6.33 / 6.54	9.29 / 9.08	144-146	90
Ic	$C_{18}H_{22}N_2O_2$	72.28 / 72.46	7.57 / 7.43	9.13 / 9.39	224-226	81
Id	$C_{15}H_{20}N_2O_2$	68.97 / 69.20	7.94 / 7.74	10.50 / 10.76	165-167	75
Ie	$C_{18}H_{24}N_2O_2$	71.67 / 71.97	8.29 / 8.05	9.19 / 9.33	203-205	92
If	$C_{13}H_{16}N_2O_2$	67.00 / 67.22	7.26 / 6.94	12.25 / 12.06	171-173	64
IIa	$C_{14}H_{18}N_2O_2$	68.10 / 68.27	7.25 / 7.37	11.21 / 11.37	155-157	83
IIb	$C_{17}H_{16}N_2O_2$	72.72 / 72.84	5.85 / 5.75	9.81 / 9.99	178-180	83
IIc	$C_{16}H_{18}N_2O_2$	71.20 / 71.09	6.59 / 6.71	10.22 / 10.36	207-209	81
IIIa	$C_{20}H_{22}N_2O_2$	74.30 / 74.51	6.70 / 6.88	8.75 / 8.69	185-187	84
IIIb	$C_{23}H_{20}N_2O_2$	77.30 / 77.51	5.96 / 5.66	7.60 / 7.86	178-180	75
IIIc	$C_{22}H_{24}N_2O_2$	75.52 / 75.83	6.72 / 6.94	8.36 / 8.04	201-203	93
IVa	$C_{16}H_{14}N_2O_3$	68.35 / 68.08	5.13 / 5.00	9.67 / 9.92	265-267	80
IVb	$C_{20}H_{14}N_2O_3$	72.50 / 72.72	4.42 / 4.27	8.30 / 8.48	230-232	77
IVc	$C_{19}H_{18}N_2O_3$	70.60 / 70.79	5.89 / 5.63	8.51 / 8.69	278-280	66
IVd	$C_{20}H_{22}N_2O_3$	70.80 / 70.99	6.80 / 6.55	8.35 / 8.28	195-196	59
IVe	$C_{19}H_{16}N_2O_3$	71.00 / 71.24	5.30 / 5.03	8.52 / 8.74	250-252	90
IVf	$C_{17}H_{16}N_2O_3$	68.68 / 68.91	5.73 / 5.44	9.11 / 9.45	205-207	87
IVg	$C_{21}H_{16}N_2O_3$	73.36 / 73.24	4.51 / 4.68	8.31 / 8.13	198-200	61
Va	$C_{11}H_{14}N_4O$	60.30 / 60.53	6.71 / 6.47	25.35 / 25.67	215-217	62
Vb	$C_{12}H_{16}N_4O$	62.30 / 62.05	6.71 / 6.94	24.33 / 24.12	186-188	76

TABLE 2. Spectral Characteristics of the Synthesized Compounds I-V

Compound	IR spectrum, ν, cm^{-1}	PMR spectrum, δ, ppm
Ia	3210, 3270, 3345 3435 (NH_2), 2183 2200 sh (CN), 1620, 1680 1710 (CO, δNH_2)	0.87 (6H, t, $2CH_3$ in R); 1.02 (6H, d, $2CH_3$) 4.23 (2H, t, CH_2 in R); 2.23 and 2.39 (4H, d and br. s, $2CH_2$); 3.15 (1H, t, 4-H); 6.86 (2H, br. s, NH_2)
Ib	3190, 3315-3390 (NH_2) 2200 (CN), 1610, 1650 1710 (CO, δNH_2)	0.96 (6H, d, $2CH_3$); 2.16 and 2.27 (4H, d and s, $2CH_2$) 2.76 (2H, t, CH_2 in R); 3.49 (1H, t, 4-H) 6.79 (2H, br. s, NH_2); 6.99 and 7.21 (5H, two m, H_{Ph})
Ic	3210, 3300, 3415 (NH_2) 2175 (CN), 1590, 1645 1665 (CO, δNH_2)	1.03 (6H, d, $2CH_3$); 1.65 and 1.95 (7H, two m, $3CH_2$ and CH in R); 2.23 and 2.42 (4H, two br. s, $2CH_2$); 3.47 (1H, m, 4-H); 5.59 (2H, br. s, CH=CH); 6.93 (2H, br. s, NH_2)
Id	3180, 3330 (NH_2) 2186 (CN), 1620, 1680 1700 (CO, δNH_2),	0.84 and 1.35 (7H, two m, R); 1.01 (6H, d, CH_3) 2.24 and 2.39 (4H, two s, $2CH_2$); 3.16 (1H, m,4-H) 6.90 (2H br. s, NH_2)
Ie	3210, 3330, 3430 (NH_2) 2189 (CN), 1600, 1650 1680 (CO, δNH_2)	1.03 (6H, d, $2CH_3$); 1.17-1.65 (11H, m, R) 2.25 and 2.43 (4H, two s, $(CH_2)_2$); 6.91 (2H, br. s, NH_2)
If	3210, 3330, 3420 (NH_2) 2230 (CN), 1635, 1680 1710 (CO, δNH_2)	1.01 and 1.10 (6H, br. s and 3H, s, CH_3) 2.23 and 2.37 (4H, two s, $3CH_2$); 3.09 (1H, q, 4-H) 6.84 (2H, br. s, NH_2)
IIa	3225, 3360 (NH_2) 2185 (CN), 1625, 1675 1710 (CO, δNH_2)	0.86 (6H, t, $2CH_3$ in R); 1.22 (2H, t, CH_2 in R) 1.81 (1H, m, CH in R); 1.93 and 2.45 (6H, two m, $3CH_2$) 3.14 (1H, t, 4-H); 6.85 (2H, br. s, NH_2)
IIb	3195, 3313, 3390 (NH_2) 2189 (CN), 1600, 1663 1680 (CO, δNH_2)	1.80-2.53 (6H, m, $3CH_2$); 2.70 (2H, t, CH_2 in R) 3.50 (1H, t, 4-H); 6.72 (2H, br. s, NH_2) 6.93 and 7.21 (5H, two m, H_{Ph})
IIc	3180, 3330 (NH_2) 2190 (CN), 1620, 1663 1695 (CO, δNH_2)	1.00-1.94 and 2.36-2.53 (13H, two m, $6CH_2$ and CH) 3.16 (1H, d, 4-H); 5.61 (2H, br. s, CH=CH) 6.94 (2H, br. s, NH_2)
IIIa	3210, 3270, 3325 3465 (NH_2), 2187 (CN), 1600, 1670 1685 (CO, δNH_2)	0.87 (6H, m, $2CH_3$); 1.25 (2H, m, CH_2 in R) 1.75 (1H, m, CH in R); 2.73 (5H, m, CH_2CHCH_2) 3.21 (1H, m, 4-H); 6.92 (2H, br. s, NH_2) 7.32 (5H, br. s, H_{Ph})
IIIb	3195, 3300-3400 (NH_2) 2190 (CN), 1620, 1670 1705 (CO, δNH_2)	2.15-2.90 (7H, m, CH_2CHCH_2 and CH_2 in R) 3.53 (1H, t, 4-H); 6.79 (2H, d, NH_2) 6.85-7.34 (10H, m, H_{Ph})
IIIc	3195, 3330, 3410 (NH_2) 2174 (CN), 1607, 1655 1680 (CO, δNH_2)	1.12-1.58 (11H, m, R); 2.50-2.90 (5H, m, $2CH_2$ and CH) 3.43 (1H, m, 4-H); 6.94 (2H, d, NH_2); 7.31 (5H, d, H_{Ph})
IVa	3180, 3300-3390 (NH_2) 2195 (CN), 1615, 1675 1720 (CO, δNH_2)	0.71 and 1.02 (6H, two d, $2CH_3$ in R) 2.00 (1H, m, CH in R); 3.32 (1H, m, 4-H) 7.30-7.88 (6H, m, NH_2 and $4H_{arom}$)
IVb	3195, 3300, 3420 (NH_2) 2187 (CN), 1610, 1640 1725 (CO, δNH_2)	2.93 (2H, two q, CH_2 in R); 3.75 (1H, t, 4-H) 6.95-7.80 (11H, m, NH_2 and $9H_{arom}$)
IVc	3150-3300, 3390 (NH_2) 2190 (CN), 1615, 1650 1690, 1740 (CO, δNH_2)	1.07-1.59 (11H, m, R); 3.28 (1H, d, 4-H) 7.33 (2H, br. s, NH_2); 7.40-7.95 (4H, m, H_{arom})
IVd	3210, 3320-3450 (NH_2) 2182 (CN), 1620, 1664 1695, 1740 (CO, δNH_2)	0.81, 1.20, and 1.64 (15H, t, br. s and m, R) 3.43 (1H, t, 4-H); 7.30 (2H, br. s, NH_2) 7.40-7.87 (4H, m, H_{arom})
Vf	3195, 3300, 3390 (NH_2) 2174 (CN), 1625,1660,1695 1735 (CO, δNH_2)	0.89 (6H, q, $2CH_3$); 1.47 (2H, t, CH_2); 1.84 (1H, m, CH) 3.39 (1H, t, 4-H); 7.30 (2H, br. s, NH_2) 7.45-7.85 (4H, m, H_{arom})
IVg	3180, 3300-3390 (NH_2) 2185 (CN), 1620, 1655 1690, 1740 (CO, δNH_2)	1.75-2.30 (4H, m, $2CH_2$); 3.53 (1H, t, 4-H) 7.12 (5H, br. s, H_{Ph}); 7.36 (2H, br. s, NH_2) 7.45-7.87 (4H, m, H_{arom})
Va	3240, 3505 (NH, NH_2) 2188 (CN), 1590 1640 (δNH_2)	0.78 (6H, t, $2CH_3$ in R); 1.80 (1H, m, CH in R) 2.17 (3H, s, CH_3); 3.36 (1H, d, 4-H); 6.77 (2H, s, NH_2) 12.01 (1H, s, NH)
Vb	3285, 3480 (NH, NH_2) 2186 (CN), 1620 1655 (δNH_2)	0.84 (6H, dd, $2CH_3$ in R); 1.46 (2H, m, CH_2 in R) 1.65 (1H, m, CH in R); 2.15 (3H, s, CH_3) 3.50 (1H, t, 4-H); 6.72 (2H, s, NH_2); 12.01 (1H, s, NH)

EXPERIMENTAL

IR spectra were recorded on an IKS-29 spectrophotometer in Nujol. ^{1}H NMR spectra of DMSO-d_6 solutions with TMS as internal standard were recorded on a Bruker WP-100 SY (100 MHz) apparatus. The course of the reactions and the purity of the products were monitored by TLC on Silufol UV-254 plates with 3:5 acetone-heptane as eluent.

Condensed Derivatives of 4-Alkyl(cycloalkyl)-2-amino-3-cyano-4H-pyrans (Ia-f, IIa-c, IIIa-c, IVa-g, Va,b). (General Method). Mixture of aldehyde VIa-i (10 mmol), malononitrile (0.66 g, 10 mmol), and N-methylmorpholine (1 ml, 10 mmol) in ethanol (15 ml) was stirred for 1 min at 20°C, then the corresponding compound VII-XI (10 mmol) was added and the mixture was kept at the same temperature for 12 h. The crystalline precipitate was filtered off and washed with ethanol and hexane.

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