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SYNTHESIS OF 3,3-DIALKYL-1-(3-PYRIDYL)-3,4-DIHYDROISOQUINOLINES

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It has been shown that the reaction of dialkylbenzylcarbinols with 3-cyano-2-pyridones and 2-chloro-3-cyanopyridines gives the corresponding 3,3-dialkyl-1-(3-pyridyl)-3,4-dihydroisoquinolines.

Keywords: dialkylbenzylcarbinols, 3,3-dialkyl-1-(3-pyridyl)-3,4-dihydroisoquinolines, 2-chloro-3-cyanopyridines, 3-cyano-2-pyridones, Ritter cyclocondensation.

The Ritter cyclocondensation reaction of nitriles with dialkylbenzylcarbinols is well known to give 3,4-dihydroisoquinolines [1-4]. We have shown the possibility of using this method for the synthesis of isoquinoline derivatives which contain heterocyclic fragments in position 1 [5, 6].

The aim of this work was the preparation of 3,4-dihydroisoquinolines containing a 2-pyridone or 2-chloropyridine substituent at position 1. The combination of two heterocyclic systems (isoquinoline and pyridine) in a single molecule opens new possibilities in chemical and pharmacological investigations. This specific target was achieved *via* the reaction of carbinols of general formula **1a-d** with 3-cyano-2-pyridones in the presence of concentrated sulfuric acid which led to the 3,3-dialkyl-1-(2-pyridon-3-yl)-3,4-dihydroisoquinolines **2a-f**. The reactions of the same carbinols with 2-chloro-3-cyanopyridines at 20ºC occurs with retention of the chlorine to give the compounds **3a-c**. The use of 2-methyl-3-(1-naphthyl)-2-propanol as the carbinol component gave the corresponding benzo[*f*]isoquinoline derivative **4**. The azomethine group in the isoquinoline ring is readily reduced by $LiAlH_4$, e.g. hydrogenation of the azomethine **2b** gives compound **5**. The synthesized compounds (Table 1) prove to be colorless, crystalline materials.

The ^1H NMR spectra of the synthesized compounds (Table 2) show proton signals for the R^1-R^4 substituents, the 4-CH_2 group in the dihydroisoquinoline ring, and the aromatic protons of the isoquinoline and pyridine rings. The protons of the two methyl groups at position 3 of the isoquinoline ring are magnetically non-equivalent and appear as two singlets, each of which corresponds to one methyl group. This differs from previously prepared 3,4-dihydroisoquinolines in whose spectra the six protons of these two groups appear as one singlet [1-6]. As is apparent from Tables 1 and 2 the nonequivalence of the methylene groups in the isoquinoline occurs in cases where there is a substituent in an *ortho* position in the pyridine ring since this increases the energetic barrier to rotation around the single bond joining the pyridine and isoquinoline rings. There also occurs a diastereotopic splitting of the 4-CH_2 group protons which appear as a doublet with $^2J = 15.4$-15.9 Hz. The corresponding splitting occurs in the spectra of the remaining materials but to a smaller degree: for compound **4** and the chloropyridine **3b** nonequivalence is only seen for the 3-CH_3 groups whereas in

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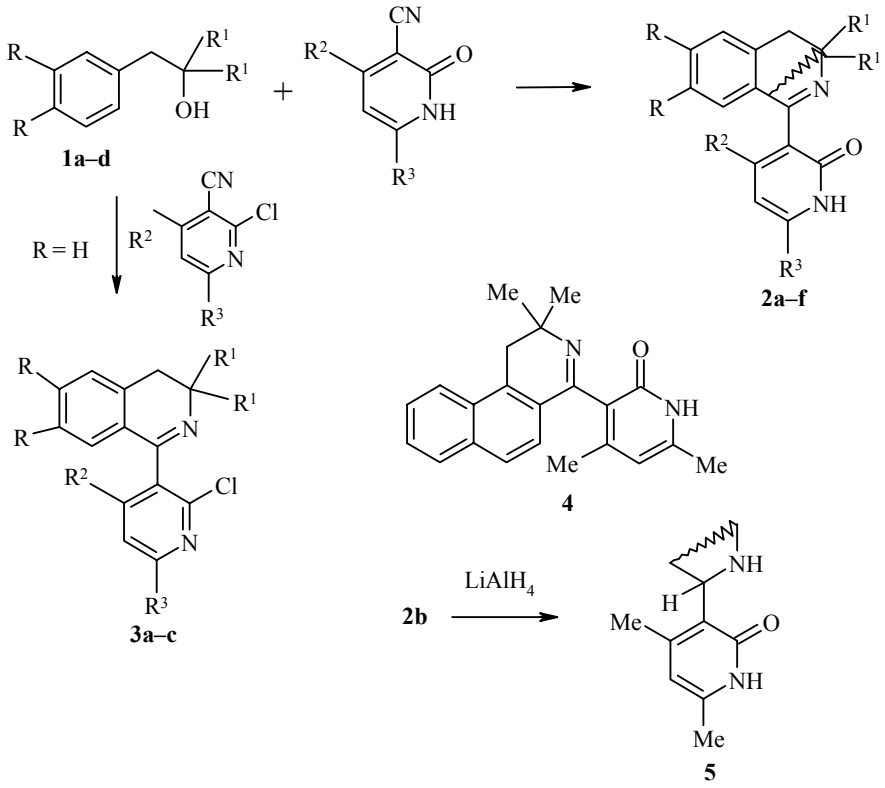

1a–d, **2a–e**, **3a–c** R = H, **2f** R = MeO; **2a–c**,**f, 3a**,**b** R^1 = Me, **2d** $R^1+R^1=(CH_2)_4$, **2e**, **3c** $R^1+R^1=(CH_2)_5$; **2a**, **3a** R^2 = H, **2b–f**, **3b**,**c** R^2 = Me; **2a**,**b**,**d–f**, **3b**,**c** R^3 = Me, **2c** R^3 = OH, **3a** R^3 = H

TABLE 1. Characteristics of the Compounds Prepared

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
2a	$C_{17}H_{18}N_2O$	76.6 / 76.7	6.7 / 6.8	10.6 / 10.5	233-235	72
2b	$C_{18}H_{20}N_2O$	77.0 / 77.1	7.1 / 7.2	10.1 / 10.0	199-200	74
2c	$C_{17}H_{18}N_2O_2$	72.2 / 72.3	6.3 / 6.4	10.0 / 9.9	208-210	68
2d	$C_{20}H_{22}N_2O$	78.3 / 78.4	7.1 / 7.2	9.2 / 9.1	118-120	57
2e	$C_{21}H_{24}N_2O$	78.6 / 78.7	7.5 / 7.6	8.8 / 8.7	228-230	56
2f	$C_{20}H_{24}N_2O_3$	70.4 / 70.6	7.0 / 7.1	8.2 / 8.2	230-232	71
3a	$C_{16}H_{15}ClN_2$	70.8 / 71.0	5.5 / 5.6	10.5 / 10.4	146-148	67
3b	$C_{18}H_{19}ClN_2$	72.3 / 72.4	6.3 / 6.4	9.5 / 9.4	86-88	58
3c	$C_{21}H_{23}ClN_2$	74.3 / 74.4	6.7 / 6.8	8.4 / 8.3	68-70	56
4	$C_{22}H_{22}N_2O$	79.8 / 80.0	6.6 / 6.7	8.6 / 8.5	158-160	73
5	$C_{18}H_{22}N_2O$	76.5 / 76.6	7.8 / 7.9	10.0 / 9.9	218-220	63

* Compound **3a** – found, %: Cl 13.0, calculated, %: Cl 13.1; **3b** – found, %: Cl 11.8, calculated, %: Cl 11.9; **3c** – found, %: Cl 10.4, calculated, %: Cl 10.5.

TABLE 2. PMR Spectra of the Compounds Prepared

Com-pound	Chemical shifts, δ, ppm (*J*, Hz)					
	$R^1 + R^1$	CH_2	pyridine ring protons	R^2, R^3 (3H, s, CH_3 and s, OH)	aromatic protons	NH, s
2a	1.3 (6H, s, 2-CH_3)	2.8 (s)	6.1 (d, *J* = 6.5, H-5'); 7.5 (d, *J* = 6.5, H-4')	2.2	7.1-7.3 (4H, m)	12.5
2b	1.2 (3H, s, CH_3); 1.4 (3H, s, CH_3)	2.7 (d, *J* = 15.8); 2.9 (d, *J* = 15.8)	5.9 (s)	2.0; 2.1	6.9-7.3 (4H, m)	12.3
2c	1.3 (6H, br. s, 2-CH_3)	2.9 (s)	5.4 (s)	1.8; 10.4	7.1-7.4 (4H, m)	11.8
2d	1.6-2.1 (8H, m, 4-CH_2)	2.8 (d, *J* = 15.9); 3.0 (d, *J* = 15.9)	6.0 (s)	2.0; 2.1	7.0-7.3 (4H, m)	12.4
2e	1.5-1.8 (10H, m, 5-CH_2)	2.9 (s)	5.9 (s)	2.0; 2.1	6.8-7.3 (4H, m)	12.4
2f*	1.2 (3H, s, CH_3); 1.4 (3H, s, CH_3)	2.7 (d, *J* = 15.4); 2.9 (d, *J* = 15.4)	5.9 (s)	1.9; 2.1	6.5 (s, H-5); 6.6 (s, H-8)	12.3
3a	1.3 (6H, s, 2-CH_3)	2.8 (s)	—*[2]	—	6.8-8.4 (7H, m)	—
3b	1.3 (3H, s, CH_3); 1.4 (3H, s, CH_3)	2.8 (s)	—*[2]	2.1; 2.4	6.7-7.3 (4H, m)	—
3c	1.3-1.7 (10H, m, 5-CH_2)	2.9 (s)	—*[2]	2.2; 2.5	6.7-7.3 (4H, m)	—
4	1.3 (3H, s, CH_3); 1.5 (3H, s, CH_3)	3.2 (s)	5.9 (1H, s)	2.0; 2.1	7.1-8.1 (6H, m)	12.6
5*[3]	1.1 (3H, s, CH_3); 1.2 (3H, s, CH_3)	2.7 (d, *J* = 11); 2.8 (d, *J* = 11)	5.8 (1H, s)	1.9; 2.2	6.8-7.2 (4H, m)	6.7, 12.5

* 3.6, s and 3.9, s (2-CH_3O).

*[2] Pyridine ring protons are found amongst the aromatic multiplet.

*[3] 5.1 ppm (br. s, 1-CHN).

the spectra of the 3-*spiro* cyclohexylisoquinolines (compounds **2e**, **3c**) splitting of the signals for protons of the 4-CH_2 groups is not observed and this may be due to the stability of a configuration which is stabilized by the repulsion of the larger volume cyclohexyl substituent. In the compounds **2a** and **3a** without a substituent in the 4 position of the pyridine ring this splitting is not seen and the signals of the corresponding methyl and methylene groups are seen as singlets.

In the spectrum of the tetrahydroisoquinoline **5** splitting of the 4-CH_2 group proton signals is also seen (d, ^2J = 11 Hz). This compound also shows a broad singlet for the 1-CHN group proton (δ 5.1) and an isoquinoline NH group proton singlet (δ 6.7 ppm).

In the IR spectra of the pyridine bases **2a-f, 4** the most intense bands are those of the carbonyl stretching vibrations for the pyridone fragment in the region 1690-1700 cm^{-1}. The spectra also contain pyridone NH group absorption bands at 3320-3340 and C=N (1620) and the spectrum of compound **2c** shows a band at 3500 cm^{-1} (OH). The spectrum of the tetrahydroisoquinoline **5** contains stretching vibrations bands for C=O and NH groups (1690 and 3320) and also for the isoquinoline ring NH at 3380 cm^{-1}.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Tesla BS-567A instrument (100 MHz) using $CDCl_3$ with HMDS (δ 0.05 ppm) as internal standard. IR spectra were taken on a Specord M-80 spectrometer using vaseline oil.

The purity of the materials prepared was checked by TLC on Silufol UV-254 plates in the system acetone–ethanol–chloroform (1:3:6) and revealed using chloranil solution in benzene (0.5%).

The compounds obtained were recrystallized from benzene (**2b**), acetonitrile (**2c**), or hexane (**2d,f, 3d-c**); the remainder were from isopropanol.

The starting carbinols are known from work in [1-6]. The corresponding nitriles were prepared by methods [7-9].

1-(4-R^2-6-R^3-2-Pyridon-3-yl)-6,7-$(R)_2$-3,3-$(R^1)_2$-3,4-dihydroisoquinolines 2a-f, 1-(4-R^2-6-R^3-2-Chloro-3-pyridyl)-3,3-$(R^1)_2$-3,4-dihydroisoquinolines 3a-c, and 2,2-Dimethyl-4-(4,6-dimethyl-2-pyridon-3-yl)-1,2-dihydrobenzo[*f*]isoquinoline (4) (General Method). The corresponding carbinol (10 mmol) was mixed with the nitrile (11 mmol) in benzene (30 ml). In the case of compound **2f** glacial acetic acid (2 ml) was added. Concentrated sulfuric acid (5 ml) was added dropwise to the above mixture at a temperature not exceeding 5ºC. The reaction mixture was stirred for 30 min at 60-70ºC, cooled to 20ºC, poured into iced water (0ºC) (100 ml), and the benzene layer was separated. The aqueous layer was neutralized with $NaHCO_3$. The precipitate formed was filtered off, dried, and recrystallized.

1-(4,6-Dimethyl-2-pyridon-3-yl)-3,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (5). A suspension of the base **2b** (1.4 g, 5 mmol) in absolute ether (70 ml) was added to a suspension of $LiAlH_4$ (0.2 g, 5 mmol) in the same solvent (70 ml). The mixture obtained was refluxed for 2 h with vigorous stirring, cooled to 20ºC, and the complex was decomposed with water (2 ml) and then with 25% ammonia (2 ml). The precipitated $Al(OH)_3$ was filtered off and washed with ether (3×50 ml). The ether solution was dried with NaOH, the solvent was distilled off, and the precipitate formed was filtered off, dried, and recrystallized.

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