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DERIVATIVES OF 1-H-2-BENZAZEPIN-1-ONE AS UNUSUAL PRODUCTS OF THE HANTSCH REACTION

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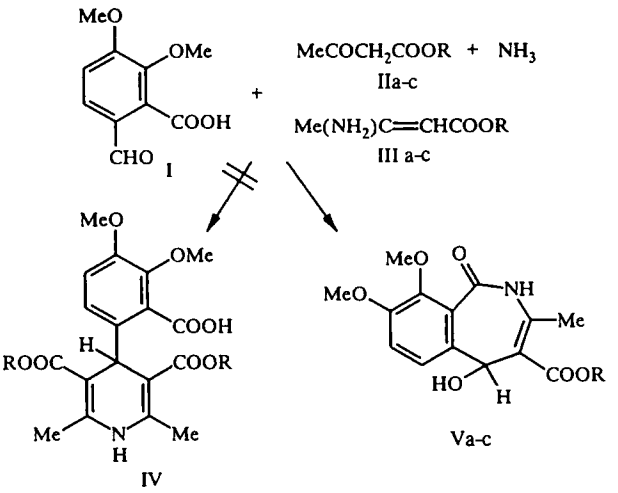
The use of opianic acid as the aldehyde component in the Hantsch reaction gives derivatives of 1-H-2-benzazepin-1-one instead of the expected 1,4-dihydropyridine derivatives.

4-Aryl-1,4-dihydropyridines hold interest since some of these compounds have cardiovascular activity [1]. In this regard, 1,4-dihydropyridine derivatives containing electron-withdrawing substituents such as a nitro group or halogen atoms in the 4-aryl group have been most thoroughly studied. Nifedipin and foridon are drugs from this class of compounds. Derivatives containing electron-donor substituents have been studied less extensively, although compounds of this type have been found, which bind selectively with adrenoreceptors [2].

In the present work, we synthesized 4-aryl-1,4-dihydropyridines containing electron-donor methoxy substituents in the 4-aryl group as well as a carboxylic acid group to improve solubility. Opianic acid (2,3-dimethoxy-6-formylbenzoic acid) (I) was used as the aldehyde component in the Hantsch synthesis of 1,4-dihydropyridines [3]. However, contrary to expectation, we obtained compounds not corresponding in their properties to 1,4-dihydropyridines IV. A study of the ^1H and ^{13}C NMR spectra indicated the 1H-2-benzazepin-1-one structure V for the products obtained.



II–V a R = Et, b R = CMe_3, c R = $(CH_2)_2OEt$

The PMR spectra of Va-Vc (Table 2) show signals at 6.2-6.3 ppm featuring long-range coupling with the aromatic 6-H proton. The coupling constant corresponds to ^4J [4] and the chemical shift differs sharply from the signal for 4-H in 1,4-dihydropyridines (5.2 ppm) [5]. Furthermore, the integral intensity shows that there is only one ester group and one methyl group. The pair of very strong signals in the vicinity of 5 and 9 ppm, which disappears upon the addition of D_2O, indicates the presence of OH and NH protons in Va-Vc. The lack of signals for a free CO_2H group may serve as additional evidence against 1,4-dihydropyridine structure. Modelling of the signals of the ^{13}C NMR spectra of Va and Vb using spherical

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TABLE 1. Physical Indices of Va-Vc

Compound	Chemical compound	mp, °C	Found, %			Calculated, %			Yield, %
			C	H	N	C	H	N	
Va	$C_{16}H_{19}NO_6$	184...186	59,54	5,85	4,12	59,81	5,96	4,36	50
Vb	$C_{18}H_{23}NO_6$	180...182	61,42	6,58	3,82	61,88	6,63	4,01	35
Vc	$C_{18}H_{23}NO_7$	132...134	58,94	6,03	3,60	59,17	6,34	3,83	42

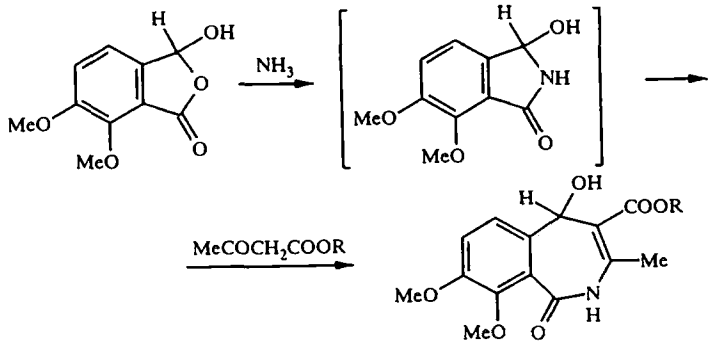
TABLE 2. PMR Spectra of Compounds Synthesized

Compound	Chemical shifts, δ, ppm and coupling constants, J, Hz							
	4-R	3-CH_3, s, 3H	8,9-OCH_3, two s, 2 × 3H	O—H, br. s	5-H d, J_{56} = 1,4	6-H, d.d, J_{AX} = 8; J_{65} = 1,4	7-H, d, J_{AX} = 8	N—H br. s,
Va	0,82 (3H, t, J = 7, $CH_2\underline{CH_3}$); 3,81 (2H, q, J = 7, $\underline{CH_2}CH_3$)	2,13	3,90 4,10	5,1	6,27	6,88	7,15	9,0
Vb	1,09 (9H, s, $C(CH_3)_3$)	2,16	3,90 4,10	5,0	6,17	6,89	7,16	9,0
Vc	1,10 (3H, t, J = 8, $CH_2\underline{CH_3}$); 3,24 (2H, t, J = 6, $CH_2\underline{CH_2}$); 3,23 (2H, q, J = 8, $\underline{CH_2}CH_3$); 3,97 (2H, t, J = 6, $\underline{CH_2}CH_2$)	2,07	3,89 4,12	5,1	6,32	6,90	7,15	8,9

substructure codes permits us to account for the shift of the signal at 78.43 ppm only to the presence of a hydroxyl group at the sp^2-hybridized carbon atom [6]. The UV spectrum lacking the band at 350 nm characteristic for the 1,4-dihydropyridine ring [5] is also evidence against 1,4-dihydropyridine structure.

The same product Va, R = C_2H_5, is obtained in both variants of the Hantsch synthesis using derivatives of acetoacetic acid II and β-aminocrotonic acid III as the carbonyl components. Products Va-Vc are colorless compounds, which readily crystallize and are quite soluble in most organic solvents.

The unusual behavior of aromatic o-aldehydoacids under conditions of the Hantsch reaction is likely a consequence of the reaction of opianic acid in the 3-hydroxynaphthalene tautomeric form similar to phthalaldehydic acid [7]:



EXPERIMENTAL

The UV spectrum was taken on a Hitachi UV-VIS 557 spectrometer in ethanol. The NMR spectra were taken on Varian Mercury 200 and Bruker WM-360 spectrometers for $CDCl_3$ solutions using TMS as the internal standard.

Ethyl Ester of 8,9-Dimethoxy-2,5-dihydro-5-hydroxy-3-methyl-1H-2-benzazepin-1-one-4-carboxylic Acid (Va). **A.** A solution of 10.51 g (0.05 mole) opianic acid I, 13.20 g (0.1 mole) ethyl acetoacetate, and 6.83 ml 25% aqueous ammonia (added in two portions with a 30 min interval) in 35 ml ethanol was heated at reflux for 4 h. After cooling, the precipitate formed was filtered off to give 8.0 g (50%) Va. Recrystallization from ethanol gave colorless needles, mp 184-186°C. UV spectrum in ethanol: λ_{max} (log ε): 208 (4.17), 274 (3.92), 310 nm (3.30). ^{13}C NMR spectrum in $CDCl_3$:

13.64 ($CH_2\underline{C}H_3$), 20.89 (3-$\underline{C}H_3$), 56.90 and 62.15 (OCH_3), 58.78 ($\underline{C}H_2CH_3$), 78.43 ($C_{(5)}$), 89.63 ($C_{(4)}$), 115.66 ($C_{(6)}$), 118.94 ($C_{(7)}$), 119.64 ($C_{(9)}$—$\underline{C}$—$C_{(1)}$), 144.67 ($C_{(9)}$), 147.89 ($C_{(5)}$—$\underline{C}$—$C_{(6)}$), 151.88 ($C_{(8)}$), 161.90 ($C_{(3)}$), 168.43 ($C_{(1)}$), 168.93 ppm ($\underline{C}O_2C_2H_5$).

Products Vb and Vc were obtained analogously from the corresponding acetoacetate esters.

^{13}C NMR spectrum of Vb: 21.09 (3-$\underline{C}H_3$), 28.05 ($C(\underline{C}H_3)_3$), 56.97 and 62.06 (OCH_3), 78.90 ($C_{(5)}$), 79.20 ($\underline{C}(CH_3)_3$), 90.35 ($C_{(4)}$), 115.54 ($C_{(6)}$), 118.82 ($C_{(7)}$), 119.84 ($C_{(9)}$—$\underline{C}$—$C_{(1)}$), 144.95 ($C_{(9)}$, 147.69 ($C_{(5)}$—$\underline{C}$—$C_{(6)}$), 151.69 ($C_{(8)}$), 161.53 ($C_{(3)}$), 168.60 ($C_{(1)}$), 168.88 ppm ($\underline{C}O_2$).

B. A solution of 10.51 g (0.05 mole) opianic acid I, 6.51 g (0.05 mole) ethyl acetoacetate II, and 6.46 g (0.05 mole) ethyl β-aminocrotonate (III) in 80 ml ethanol was heated at reflux for 5 h. After cooling, the crystalline precipitate was filtered off to give 3 g (19%) Va.

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