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Substituted Tetrahydropyridine and Dihydropyridobenzoxazine Ring Syntheses

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Synopsis. The ternary condensation of ethyl acetoacetate, 3-methoxysalicylaldehyde, and substituted benzaldehydes in the presence of ammonium acetate gave 1,2,5,6-tetrahydropyridine (**1**) and 6*H*-8,9-dihidropyrido[1,2-*c*][1,3]-benzoxazine (**2**) derivatives.

We have previously shown[1] that the reaction of ethyl acetoacetate with substituted salicylaldehydes gives heterocyclic products which contain two salicylaldehyde residues. However, the ternary condensation of ethyl acetoacetate, 3-methoxysalicylaldehyde, and benzaldehyde derivatives was found to produce compounds containing salicylaldehyde and benzaldehyde residues. In this reaction, the use of *m*-nitrobenzaldehyde as the aldehyde reactant afforded a mixture of **1** and **2** or exclusively **2**, depending on the conditions. Attempts to isolate an intermediate from the reaction of 3-methoxysalicylaldehyde with 2,4-dichlorobenzaldehyde in ethanol gave a yellow crystalline solid. The elemental analysis and NMR spectral data of this substance are compatible with the structure **3** (R_1=R_3=Cl, R_2=H).

The mode of formation of the compound **1** can be concluded as follows. Two molecules of 3-methoxysalicylaldehyde and one of substituted benzaldehyde condense with ammonia to yield **3**. Then, **3** (which undergoes C–N bond cleavage) reacts to ethyl acetoacetate to form **1**. In support of this, treatment of ethyl acetoacetate with **3** (R_1=R_3=Cl, R_2=H) in the presence of ammonium acetate gave the compound **1e**. The compound **2** could be formed by further condensation of **1a** with another molecule of *m*-nitrobenzaldehyde.

Experimental

4-Amino-6-aryl-3-ethoxycarbonyl-2-(2-hydroxy-3-methoxyphenyl)-1,2,5,6-tetrahydropyridines (1). To a mixture of ethyl acetoacetate (0.05 mol), 3-methoxysalicylaldehyde (0.05 mol), and substituted benzaldehyde (0.05 mol) in ethanol (15 ml), ammonium acetate (0.05—0.06 mol) was added and the mixture was refluxed for 1—2 hr. The solid that separated on cooling was recrystallized from ethanol–dimethyl sulfoxide.

*10-Amino-11-ethoxycarbonyl-4-methoxy-6,8-bis(3-nitrophenyl)-6*H*-8,9-dihydropyrido[1,2-*c*][1,3]benzoxazine (2).* Ammo-

TABLE 1. COMPOUNDS **1a-e** AND **2**

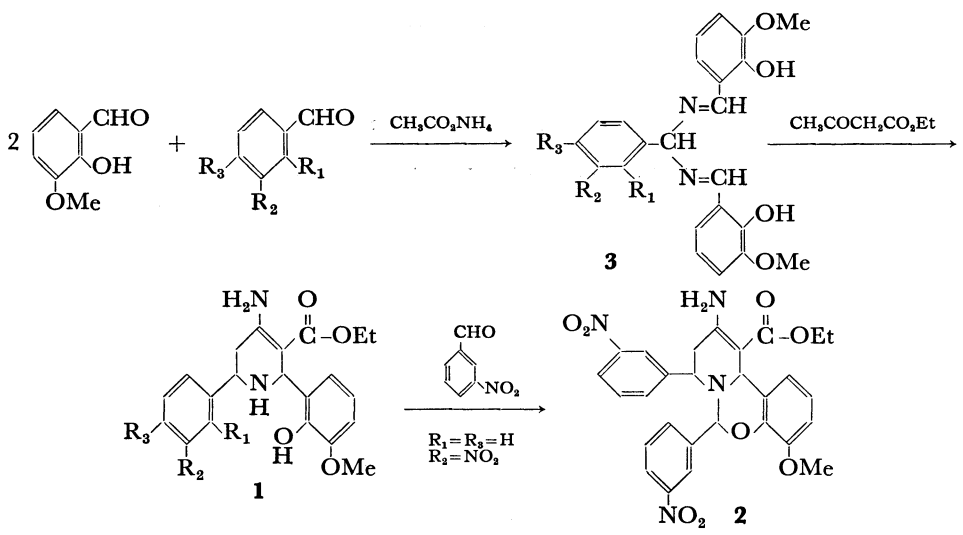
Compound	R_1	R_2	R_3	Yield (%)	Mp (°C) (dec)	Formula	Analysis %					
							Found			Calcd		
							C	H	N	C	H	N
1a[a]	H	NO_2	H	13[a]	189—190	$C_{21}H_{23}N_3O_6$	61.18	5.62	10.12	61.01	5.61	10.16
1b	H	H	NO_2	46	197—198	$C_{21}H_{23}N_3O_6$	60.84	5.60	10.30	61.01	5.61	10.16
1c	H	H	Br	12	205—206	$C_{21}H_{23}N_2O_4Br$	56.45	5.13	6.30	56.37	5.14	6.26
1d	H	H	CN	8	209—210	$C_{22}H_{23}N_3O_4$	67.35	5.93	10.52	67.16	5.89	10.68
1e	Cl	H	Cl	19	187—189	$C_{21}H_{22}Cl_2N_2O_4$	57.59	5.04	6.61	57.67	5.03	6.41
2				30	211—212	$C_{28}H_{26}N_4O_8$	61.33	4.86	10.22	61.53	4.80	10.25

a) This substance was obtained along with 2 (13.5% yield).

TABLE 2. IR AND NMR DATA FOR THE COMPOUNDS **1a**, **1e**, AND **2**

Compound	IR[a] (ν_{max}, cm^{-1})	NMR[b] δ, (ppm)
1a	3440, 3330 (NH_2), 3280 (NH), 1665 (C=O)	0.92 (t, 3H, ester CH_3), 2.78 (d, 2H, $-C\underline{H}_2-CH\langle$), 3.76 (s, 3H, OCH_3), 4.0 (q, 2H, ester CH_2), 4.24 (t, 1H, $-CH_2C\underline{H}\langle$), 5.24 (s, 1H, $-NH-C\underline{H}\langle$), 6.6—6.9 (m, 3H, aromatic), 7.4—8.3 (m, 6H, aromatic and NH_2)
1e	3410, 3310 (NH_2), 3280 (NH), 1665 (C=O)	0.88 (t, 3H, ester CH_3), 3.0 (d, 2H, $-C\underline{H}_2-CH\langle$), 3.66 (s, 3H, OCH_3), 4.0 (q, 2H, ester CH_2), 4.56 (t, 1H, $-CH_2-C\underline{H}\langle$), 5.83 (s, 1H, $-NH-C\underline{H}\langle$), 6.8—7.5 (m, 6H, aromatic), 7.7—8.4 (b, 2H, NH_2)
2	3470, 3350 (NH_2), 1670 (C=O)	0.88 (t, 3H, ester CH_3), 3.0 (d, 2H, $-C\underline{H}_2-CH\langle$), 3.8 (q, 2H, ester CH_2), 3.86 (s, 3H, OCH_3), 4.15 (t, 1H, $-CH_2-C\underline{H}\langle$), 4.82 (s, 1H, $\rangle N-CH\langle$), 6.1 (s, 1H, $\rangle N-\overset{|}{C}H-O-$), 6.6—7.0 (m, 3H, aromatic), 7.6—8.3 (m, 10H, aromatic and NH_2)

a) IR spectra were recorded for KBr disks. b) NMR spectra were determined in deuteriopyridine with tetramethylsilane as internal reference; s, singlet; d, doublet; t, triplet; q, quartet; b, broad; m, multiplet.



3

1

2

nium acetate (0.06 mol) was added to a mixture of ethyl acetoacetate (0.05 mol), 3-methoxysalicylaldehyde (0.05 mol), and *m*-nitrobenzaldehyde (0.05 mol) in ethanol (10 ml) and the mixture was heated under reflux for 2 hr. The reaction mixture was left at room temperature for several days, when yellow crystals were formed. The same reaction under reflux for 1 hr afforded a mixture of **1a** (13%) and **2** (13.5%). **2** was also prepared in 60% yield from the reaction of **1a** and *m*-nitrobenzaldehyde by refluxing with ammonium acetate in ethanol.

α,α-Bis(3-methoxysalicylideneamino)-2,4-dichlorotoluene (3, $R_1=R_3=Cl$, $R_2=H$). To a mixture of 3-methoxysalicylaldehyde (2.0 g) and 2,4-dichlorobenzaldehyde (2.3 g) in ethanol (15 ml), ammonium acetate (1.0 g) was added and the mixture was heated under reflux for 0.5 hr. After cooling, water (3 ml) was added to the reaction mixture and the solution was left to cool for several days, a crystalline yellow solid separated; yield: 1.0 g; mp 135—136 °C (from ethanol).

Found: C, 59.93; H, 4.74; Cl, 15.26; N, 5.87%. Calcd for $C_{23}H_{20}Cl_2N_2O_4$: C, 60.13; H, 4.35; Cl, 15.45; N, 6.10%. NMR ($CDCl_3$): δ 3.88 (s, 6H, 2 OCH_3), 6.38 (s, 1H, =N-CH-N=), 6.8—7.1 (m, 6H, aromatic), 7.2—7.4 (m, 3H, aromatic), 8.56 (s, 2H, 2 -N=CH-), 12.84—13.24 (broad, 2H, 2 OH).

Heating this product with ethyl acetoacetate and ammonium acetate in ethanol for 1 hr gave the compound **1e** in 42% yield.

Reference

1) A. Sakurai and H. Midorikawa, *J. Chem. Soc., Perkin I*, **1975**, 2025.