Pyridazines. LI [1]. On the Reactivity of Pyridazinecarbaldehydes towards Selected Active-Hydrogen Compounds

Wolfgang Dostal [2], Gottfried Heinisch*, Wolfgang Holzer,
Ingrid Perhauc [3] and Changtu Zheng

Institute of Pharmaceutical Chemistry, University of Vienna,
Währinger Straße 10, A-1090 Vienna, Austria

Received January 9, 1990

Dedicated with best personal wishes to Professor Dr. F. Sauter on the occasion of his 60th anniversary

Reactions of 3-pyridazinecarbaldehyde and 4-pyridazinecarbaldehyde with various active methylene carbanions were studied. The products obtained in Knoevenagel reactions, Wittig-Horner-Emmons reactions, and Hantzsch-type reactions are presented.

J. Heterocyclic Chem., **27**, 1313 (1990).

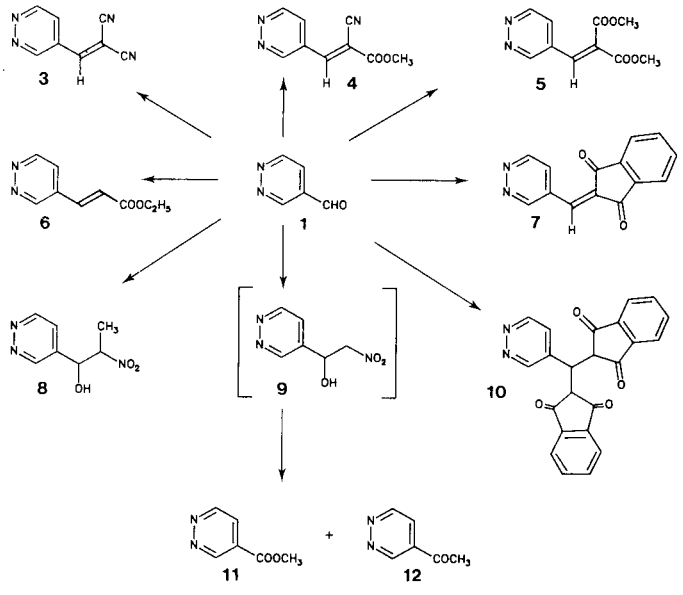
Whereas numerous *N*-heteroaromatic carbaldehydes are extensively used as versatile synthetic building blocks, the chemistry of pyridazinecarbaldehydes so far has not been studied in detail. Previously, we have reported the first synthesis of both monoformylpyridazines, namely 3-pyridazinecarbaldehyde (**2**) [4] and 4-pyridazinecarbaldehyde (**1**) [5,6]. In reactions with a limited number of active-hydrogen compounds (acetone, cyclohexanone, 3-methylpyridazine, 4-methylpyridazine) it was observed that addition of carbanions to the carbonyl group in **1** and **2** in general takes place smoothly [4,5]. However, we encountered problems, in particular with 4-pyridazinecarbaldehyde (**1**), in attempts to obtain the corresponding condensation products owing to a pronounced tendency of the intermediate pyridazinylcarbinols to dismutate at elevated temperatures [5,7]. Thus, at least in this respect the behaviour of formylpyridazines differs markedly from that of carbaldehydes derived from other six-membered azaaromatic systems like pyridine, pyrazine or pyrimidine.

In an extension of our previous investigations we here report on the products obtained from **1** and **2** upon treatment with a variety of active-hydrogen compounds under the conditions of Knoevenagel-, Wittig-Horner-Emmons- and Hantzsch-type reactions.

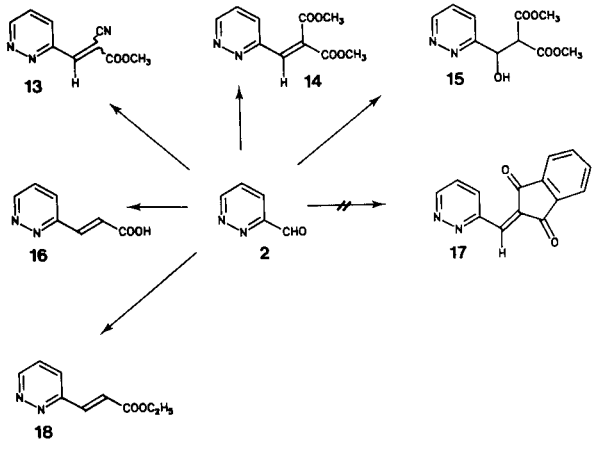
Reaction of 4-pyridazinecarbaldehyde (**1**) with malononitrile in ethanol solution was found to proceed smoothly at room temperature to give the condensation product **3** in 80% yield [8]. Under such mild conditions also reaction of **1** with methyl cyanoacetate affording compound **4** (yield 63%) takes place [8]. The *E*-configuration of **4** as given in Scheme 1 follows unambigously from the ^{1}H-coupled ^{13}C nmr spectrum, as the vicinal coupling constant of the olefinic proton with the nitrile carbon atom is considerably larger (14.0 Hz) than that with the ester carbonyl C-atom (6.8 Hz). Whereas these reactions proceed without a catalyst, the preparation of the condensation product **5** from **1** and dimethyl malonate was found to require the presence of piperidine and elevated temperature.

In contrast to the 4-pyridazinyl series, attempts to react 3-pyridazinecarbaldehyde (**2**) with malononitrile under various reaction conditions failed [9]. However, we succeeded in the preparation of the condensation product **13** from **2** and methyl cyanoacetate in high yield. Other than with **1**, in this case the reaction occurs only when performed in the presence of catalytic amounts of triethylamine. Attempts to establish the configuration of compound **13** *via* the ^{1}H-coupled ^{13}C nmr spectrum, however, failed owing to insufficient solubility. Diethylamine was found to be a suitable catalyst for the reaction of **2** with dimethyl malonate. Depending on the reaction conditions applied the alcohol **15** or the condensation product **14** could be obtained (methanol/−10°: formation of **15**, dichloromethane/20°: formation of **14**).

Scheme 1



Scheme 2



Preparation of 3-(4-pyridazinyl)acrylic acid by refluxing **1** with malonic acid in pyridine solution has been reported [5]. Under analogous conditions we now obtained *E*-3-(3-pyridazinyl)acrylic acid (**16**) [10] in 27% yield from **2**. The corresponding ethyl esters **6** and **18** turned out to be conveniently accessible from pyridazinecarbaldehydes **1** and **2**, respectively, under conditions of the Wittig-Horner-Emmons reaction (treatment with triethyl phosphonoacetate/sodium hydride in DMF solution). The *E*-configuration of compounds **16**, **6**, and **18** unambigously follows from the magnitude of the coupling constant of the olefinic protons. For the reactivity of carbaldehydes **1** and **2** towards phosphorus ylides compare ref [12].

Tlc-monitoring revealed that in the presence of catalytic amounts of diethylamine both formylpyridazines **1** and **2** add nitroalkanes like nitromethane or nitroethane spontaneously even at −20°. From the reaction of **1** with nitroethane a crystalline precipitate was obtained in 87% yield which after recrystallization from ethanol gave a product with the elemental composition $C_7H_9N_3O_3$, consistent with the addition product **8**. No attempts were made to separate this mixture of four stereoisomers. In contrast, we failed in the isolation of the nitroalkanol **9** initially formed from **1** and nitromethane. Owing to its instability even at −20°, only decomposition products **11** and **12** could be detected by means of tlc and gc/ms after careful workup of the reaction mixture. The formation of methyl 4-pyridazinyl ketone (**12**) may be interpreted in terms of HNO_2-elimination from **9**. The tendency of 1-(4-pyridazinyl)-2-nitroalkanols to eliminate nitrous acid is further indicated by the fact that the mass spectrum of the homologous nitroalkanol **8** exhibits a peak at m/z = 136, attributable to the loss of a HNO_2-fragment from the molecular ion. No definitive conclusions can be drawn presently with regard to the formation of methyl 4-pyridazinecarboxylate (**11**). Presumably, compound **11** results from oxidation of the hemiacetal of **1** (formed from **9** by retro-aldol reaction and subsequent addition of methanol) during workup. As an indication for the tendency of compounds of type **9** and **8** to undergo retro-aldol reaction the base peak in the mass spectrum of **8** (observed at m/z = 108) resulting from such a process may serve. From the mixtures obtained upon reaction of 3-pyridazinecarbaldehyde (**2**) with nitroethane or nitromethane, respectively, so far no analytically pure materials could be isolated.

The reported anticoagulant activity of 2-(pyridylmethylene)indan-1,3-diones [13] prompted us to investigate also the reaction of **1** with 1,3-indandione. Initial attempts to perform the reaction in ethanol solution at room temperature (piperidine as catalyst) resulted in a 43% yield of a product $C_{23}H_{14}N_2O_4$, for which the structure **10** has to be assigned according to the ^1H nmr spectrum (AB_2 spin system in the aliphatic region) and the ms data (base peak at m/z = 146 attributable to an indandione unit resulting from retro-Michael reaction). However, when this reaction was run in dichloromethane solution (room temperature, piperidine as catalyst) the target condensation product **7** was obtained in high yield (70%). In contrast, we so far could not find out reaction conditions permitting the preparation of the condensation product **17**, starting from 3-pyridazinecarbaldehyde (**2**) and 1,3-indandione.

Even in the presence of a catalyst [14] the carbaldehydes **1** and **2** were found to react with β-ketoesters like methyl

Scheme 3

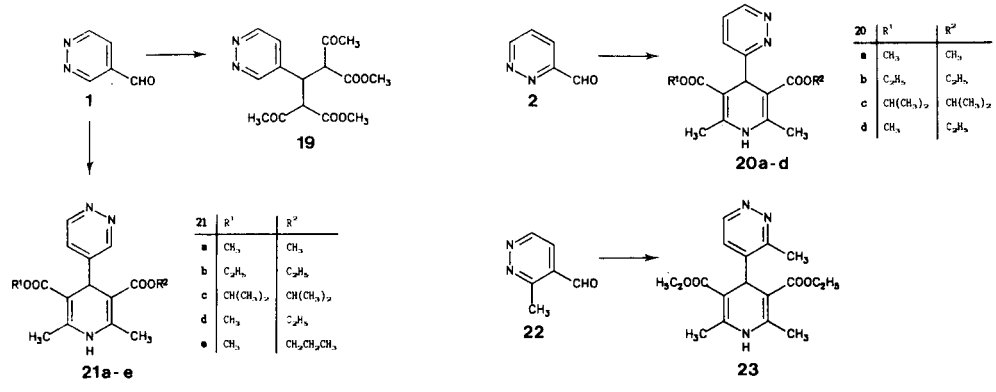


Table 1

Analytical Data and Yields of Compounds Prepared

Compound No.	Molecular Formula (Mol.Mass)	Elemental Analysis (%) (Calcd./Found) C	H	N	Yield (%)	Mp (°C)	Recryst. Solvent
3	$C_8H_4N_4$ (156.15)	61.54 61.24	2.58 2.75	35.88 35.92	80	144-148 dec	ethanol
4	$C_9H_7N_3O_2$ (189.17)	57.14 56.96	3.73 3.79	22.21 21.96	63	122-123	ethyl acetate - light petroleum
5	$C_{10}H_{10}N_2O_4$ (222.20)	54.05 53.93	4.54 4.44	12.61 12.52	24	48-49	diisopropyl ether
6	$C_9H_{10}N_2O_2$ (178.19)	60.66 60.77	5.66 5.71	15.72 15.56	49	85	diisopropyl ether
7	$C_{14}H_8N_2O_2$ (236.24)	71.18 71.16	3.41 3.24	11.86 11.87	70	143-145 dec	ethanol
8	$C_7H_5N_3O_3$ (183.17)	45.90 46.29	4.95 5.03	22.94 22.79	87	126-127 dec	ethanol
10	$C_{23}H_{14}N_2O_4$ (382.39)	72.24 72.01	3.69 3.80	7.32 7.12	43	184-185	methanol
13	$C_9H_7N_3O_2$ (189.17)	57.14 56.93	3.73 3.83	22.21 22.31	87	166-169 dec	methanol
14	$C_{10}H_{10}N_2O_4$ (222.20)	54.05 53.98	4.54 4.57	12.61 12.54	30	83-84	ethyl acetate - light petroleum
15	$C_{10}H_{12}N_2O_5$ (240.22)	50.00 50.25	5.04 5.13	11.66 11.56	45	79-81	ethyl acetate - light petroleum
16	$C_7H_6N_2O_2$ (150.14)	---------- ----------			27	245* dec	------
18	$C_9H_{10}N_2O_2$ (178.19)	60.66 60.68	5.66 5.63	15.72 15.64	44	47-48	------
19	$C_{15}H_{18}N_2O_6$ (322.32)	55.90 55.83	5.63 5.63	8.69 8.59	44	122-124	methanol
20a	$C_{15}H_{17}N_3O_4$ (303.32)	59.40 59.50	5.65 5.59	13.85 13.94	49	233-234	methanol
20b	$C_{17}H_{21}N_3O_4$ (331.37)	61.62 61.30	6.39 6.20	12.68 12.57	22	186-187	ethanol
20c	$C_{19}H_{25}N_3O_4$ (359.43)	63.49 63.30	7.01 6.84	11.69 11.66	28	198-199	methanol - water
20d	$C_{16}H_{19}N_3O_4$ (317.35)	60.56 60.49	6.04 6.09	13.24 13.39	52	173-175	ethanol - water
21a	$C_{15}H_{17}N_3O_4$ (303.32)	59.40 59.40	5.65 5.70	13.85 13.77	34	240-241 dec	methanol
21b	$C_{17}H_{21}N_3O_4$ (331.37)	61.62 61.40	6.39 6.28	12.68 12.62	21	226-227	ethanol
21c	$C_{19}H_{25}N_3O_4$ (359.43)	63.49 63.70	7.01 6.75	11.69 11.76	32	252-253	ethanol
21d	$C_{16}H_{19}N_3O_4$ (317.35)	60.56 60.45	6.04 6.10	13.24 13.22	40	218-220	ethyl acetate - light petroleum
21e	$C_{17}H_{21}N_3O_4$ (331.37)	61.62 61.93	6.39 6.47	12.68 12.24	46	203-207	methanol - water
23	$C_{18}H_{23}N_3O_4$ (345.40)	62.59 62.39	6.71 6.66	12.17 12.10	32	226-227	methanol

* Literature mp [11]: 223-224° dec.

Table 2

Spectral Data of Compounds Prepared

Compound No.	IR (KBr) ν(cm^{-1})	MS (m/z, %) (M^+, base peak)	Sol-vent*	^{1}H-NMR δ (ppm) Pyridazine Protons				Other Protons
				H-3	H-4	H-5	H-6	
3	2240 (C≡N)	156 (78) 101 (100)	a	9.45	-	8.10	9.55	7.83 (s, 1 H, olefinic H)
4	2235 (C≡N) 1730 (C=O)	189 (100)	b	9.56	-	8.15	9.50	8.49 (s, 1 H, olefinic H), 3.90 (s, 3 H, OCH_3)
5	1720 (C=O)	222 (32) 179 (100)	a	9.17	-	7.45	9.25	7.65 (s, 1 H, olefinic H), 3.90 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3)
6	1700 (C=O)	178 (100)	b	9.51	-	7.94	9.26	7.60 (A-part of an AB-system, J = 16.2 Hz, 1 H, olefinic H-3), 7.02 (B-part of an AB-system, J = 16.2 Hz, 1 H, olefinic H-2), 4.19 (q, J = 7.1 Hz, 2 H, OCH_2), 1.23 (t, J = 7.1 Hz, 3 H, CH_3)
7	1730 (C=O) 1690 (C=O)	236 (9) 208 (100)	b	9.80	-	8.44	9.47	8.02 (m, 4 H, benzene-H), 7.85 (s, 1 H, olefinic H)
8	3160 (OH)	183 (18) 108 (100)	b	9.50	-	7.80	9.30	6.60 (d, J = 6 Hz, 1 H, OH^+), 5.05 (m, 2 H, CH-CH), 1.35 (d, J = 7 Hz, 3 H, CH_3)
10	1730 (C=O) 1700 (C=O)	382 (0.1) 146 (100)	a	9.22	-	7.59	9.10	7.88 (m, 8 H, benzene-H), 4.27 (A_2-part of an A_2B-system, 2 H, CO-CH-CO), 3.90 (B-part of an A_2B-system, 1 H, -$\underset{|}{C}$H-)
13	2220 (C≡N) 1710 (C=O)	189 (16) 159 (100)	b	-	8.20	7.90	9.36	8.53 (s, 1 H, olefinic H), 3.91 (s, 3 H, OCH_3)
14	1725 (C=O) 1700 (C=O)	222 (36) 191 (100)	a	-	7.40-7.70		9.20	7.80 (s, 1 H, olefinic H), 3.92 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3)

15	3120 (OH) 1740 (C=O) 1720 (C=O)	240 (2) 101 (100)	a	-	7.85	7.52	9.20	5.70 (d, J = 4.5 Hz, 1 H, CH-O), 4.50 (d, J = 4.5 Hz, 1 H, CH-C), 3.80 (s, 3 H, OCH_3), 3.70 (s, 3 H, OCH_3)
16	1710 (C=O)	150 (100) 105 (62)	c	-	7.60-7.80		9.00	7.15 (A-part of an AB-system, J = 16 Hz, 1 H, olefinic H-3), 6.61 (B-part of an AB-system, J = 16 Hz, 1 H, olefinic H-2)
18	1690 (C=O)	178 (72) 106 (100)	b	-	8.10	7.72	9.19	7.75 (A-part of an AB-system, J = 16.1 Hz, 1 H, olefinic H-3), 7.03 (B-part of an AB-system, J = 16.1 Hz, 1 H, olefinic H-2), 4.20 (q, J = 7.2 Hz, 2 H, OCH_2), 1.24 (t, J = 7.2 Hz, 3 H, CH_3)
19	1735 (C=O) 1710 (C=O)	322 (25) 43 (100)	b	9.05	-	7.40	9.05	compare reference [18]
20a	3200 (NH) 1695 (C=O)	303 (4) 224 (100)	b	-	7.60-8.00		9.20	9.30 (s, broad$^+$, 1 H, NH), 5.25 (s, 1 H, pyridine H-4), 3.60 (s, 6 H, OCH_3), 2.20 (s, 6 H, pyr-CH_3)
20b	3200 (NH) 1695 (C=O) 1685 (C=O)	331 (21) 253 (100)	a	-	7.80	7.45	9.20	9.20 (s$^+$, 1 H, NH), 5.30 (s, 1 H, pyridine H-4), 4.15 (q, 4 H, OCH_2), 2.30 (s, 6 H, pyr-CH_3), 1.15 (t, 6 H, CH_2-$\underline{CH_3}$)
20c	3200 (NH) 1680 (C=O)	359 (8) 196 (100)	a	-	7.70	7.35	9.05	9.35 (s, broad$^+$, 1 H, NH), 5.30 (s, 1 H, pyridine H-4), 4.95 (m, 2 H, OCH), 2.20 (s, 6 H, pyr-CH_3), 1.20 (m, 12 H, OCH-$\underline{CH_3}$)
20d	3200 (NH) 1680 (C=O)	317 (8) 238 (100)	a	-	7.70	7.40	9.10	9.25 (s, broad$^+$, 1 H, NH), 5.25 (s, 1 H, pyridine H-4), 4.10 (q, J = 7.5 Hz, 2 H, OCH_2), 3.60 (s, 3 H, OCH_3), 2.20 (s, 6 H, pyr-CH_3), 1.20 (t, J = 7.5 Hz, 3 H, CH_2- $\underline{CH_3}$)
21a	3170 (NH) 1670 (C=O)	303 (3) 224 (100)	b	9.20	-	7.40	9.10	9.00 (s, broad$^+$, 1 H, NH), 4.87 (s, 1 H, pyridine H-4), 3.60 (s, 6 H, OCH_3), 2.30 (s, 6 H, pyr-CH_3)
21b	3200 (NH) 1700 (C=O)	331 (2) 252 (100)	a	9.20	-	7.40	9.10	6.60 (s, broad$^+$, 1 H, NH), 5.05 (s, 1 H, pyridine H-4), 4.10 (q, 4 H, OCH_2), 2.40 (s, 6 H, pyr-CH_3), 1.25 (t, 6 H, CH_2-$\underline{CH_3}$)
21c	3190 (NH) 1690 (C=O)	359 (5) 280 (100)	a	9.20	-	7.40	9.10	6.70 (s, broad$^+$, 1 H, NH), 5.00 (s, 1 H, pyridine H-4), 4.95 (m, 2 H, $\underline{CH}$-CH_3), 2.40 (s, 6 H, pyr-CH_3), 1.20 (m, 3 H, CH-$\underline{CH_3}$)

21d	3190 (NH)	317 (9)	a	9.25	-	7.40	9.10	7.50 (s, broad[+], 1 H, NH), 5.08 (s, 1 H, pyridine H-4), 4.15 (q, 2 H, OCH_2), 3.65 (s, 3 H, OCH_3), 2.40 (s, 6 H, pyr-CH_3), 1.23 (t, 3 H, CH_2-$\underline{CH_3}$)
	1690 (C=O)	238 (100)						
21e	3190 (NH)	331 (2)	a	9.25	-	7.40	9.10	6.90 (s, broad[+], 1 H, NH), 5.05 (s, 1 H, pyridine H-4), 4.02 (m, 2 H, OCH_2), 3.67 (s, 3 H, OCH_3), 2.40 (s, 6 H, pyr-CH_3), 1.70 (m, 2 H, CH_2-$\underline{CH_2}$-CH_3), 1.05 (m, 3 H, CH_2-$\underline{CH_3}$)
	1690 (C=O)	252 (100)						
23	3180 (NH)	345 (2)	a	-	-	7.50	9.00	7.80 (s, broad[+], 1 H, NH), 5.20 (s, 1 H, pyridine H-4), 4.12 (q, 4 H, OCH_2), 3.00 (s, 3 H, pyridazine-CH_3), 2.35 (s, 6 H, pyr-CH_3), 1.20 (t, 6 H, CH_2-$\underline{CH_3}$)
	1680 (C=O)	252 (100)						

a: Deuteriochloroform, b: deuteriodimethyl sulfoxide, c: deuterium oxide - sodium deuteroxide.

The pyridazine protons always occur as ABX spin-systems (except comp. **23**) with typical coupling constants. 3-Substituted pyridazine derivatives: ^3J(H-4,H-5)~ 8.5 Hz, ^4J(H-4,H-6)~ 1.6 Hz, ^3J(H-5,H-6)~ 5.0 Hz; 4-substituted pyridazine derivatives: ^4J(H-3,H-5)~ 2.3 Hz, ^5J(H-3,H-6)~ 1.3 Hz, ^3J(H-5,H-6)~ 5.3 Hz.

† Exchangeable with deuterium oxide.

acetoacetate only at elevated temperature. In the case of **2** we did not succeed in the isolation of a defined reaction product from the resulting multi-component mixture. Elemental analysis and ms data of product **19**, obtained in 44% yield after refluxing **1** with methyl acetoacetate in methanol solution, revealed the compound to be a 1:2 adduct. Attempts to suppress additional Michael-reaction in this case met with failure. It has to be mentioned that also in the pyridinecarbaldehyde series such addition-reactions of 1:1 condensation products occur occasionally [15].

In view of the therapeutic importance of dialkyl 4-aryl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylates as calcium antagonistic agents [19] investigation of the reactivity of pyridazinecarbaldehydes **1** and **2** under conditions of the Hantzsch-type dihydropyridine synthesis became an object of our interest as well. Despite the fact that in search of more efficaceous agents the aryl-substituent in these widely used drugs has been replaced by a variety of heteroaromatic systems [20,21] (including also pyridine), to our knowledge there is no report available on the synthesis of 1,2-diazine-derived congeners.

By reacting **1** or **2** with a twofold molar amount of the appropriate alkyl acetoacetate in the presence of an excess of ammonia we succeeded in the preparation of the novel pyridazinyldihydropyridines **21a-c** and **20a-c**, respectively, in moderate to satisfactory yields. As shown in an experiment using 3-methyl-4-pyridazinecarbaldehyde (**22**) [6] which gave compound **23** in comparable yield, also formylpyridazines additionally bearing a highly activated alkyl group can be employed for the construction of a 1,2-diazinyl-substituted dihydropyridine system without alteration of the reaction course.

The continuing interest in unsymmetrically substituted 4-aryldihydropyridines (two different ester functions attached to C-3 and C-5 like in Nisoldipine [22] or Felodipine [23]) prompted us to attempt also the synthesis of such types of compounds substituted at C-4 by a pyridazine-core. Bearing in mind the above mentioned problems encountered with Knoevenagel condensation products of **1** or **2** and β-ketoesters, a one-pot procedure consisting of reaction of the carbaldehyde with an alkyl acetoacetate and an alkyl 3-aminocrotonate [24] was employed. Under these conditions we obtained a 46% yield of analytically pure "mixed" dicarboxylate **21e** from **1**, *n*-propyl acetoacetate, and methyl 3-aminocrotonate. However, hplc investigations of the crude products obtained from reaction of **1** or **2** with methyl acetoacetate and ethyl 3-aminocrotonate revealed that in addition to the target compounds **21d** and **20d** considerable amounts of "symmetrical" dicarboxylates, **21a** and **21b**; **20a** and **20b**, had been formed as by-products. Initial attempts to separate these mixtures of closely related substances in a preparative scale failed. Whereas the diethyl dicarboxylates **21b** and

20b obviously result from reactions of **1** or **2** with two mole-equivalents of the enaminoester, the formation of the dimethyl dicarboxylates **21a** and **20a** may be explained by reaction of **1** or **2** with methyl acetoacetate and ammonia eliminated in the course of the formation of compounds **21b** and **20b**, respectively [25]. Thus to suppress these side-reactions, a procedure characterized by dropwise addition of ethyl 3-aminocrotonate to a boiling solution of **1** or **2** and methyl acetoacetate was chosen which indeed afforded satisfactory yields of pure samples (purity >95% according to hplc analysis) of the desired "unsymmetrical" dicarboxylates, **21d**: 40%; **20d**: 52%.

Structure proof for all newly synthesized compounds rests on elemental analyses (Table 1) as well as on spectroscopic data (Table 2).

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage microscope and are uncorrected. The ir spectra (potassium bromide) were recorded on a Jasco IRA-1 spectrometer. The mass spectra were obtained on a Varian MAT 311A spectrometer (70 eV), glc/ms analyses were carried out on a Hewlett-Packard 5890A/-5970B-GC/MSD instrument. The ^{1}H nmr spectra were obtained either on a Varian EM 390 (90 MHz) or on a Bruker AC 80 (80 MHz) instrument, ^{13}C nmr spectra were recorded on a Bruker AC 80 (20 MHz for ^{13}C); chemical shifts are reported in ppm downfield from tetramethylsilane as an internal standard and are given in δ units. For analytical tlc, DC-Alufolien, Kieselgel 60 F_{254} (Merck) were used. Column chromatography was performed on Kieselgel 60 (70-230 mesh, Merck), medium pressure liquid chromatography (mplc) in Lobar^R glass columns filled with 250 g of LiChroprep^R Si 60 (Merck). Hplc analyses were carried out on a Kontron 420 instrument equipped with an Uvikon 735 LC uv-detector and FZ Seibersdorf columns filled with LiChrosorb RP 18, 5μm). Elemental analyses were carried out by Mikroanalytisches Laboratorium (Dr. J. Zak), Institute of Physical Chemistry, University of Vienna.

(4-Pyridazinylmethylene)malononitrile (**3**).

To a stirred solution of 216 mg (2 mmoles) of **1** in 1 ml of dry ethanol 190 mg (2.9 mmoles) of malononitrile was added over a period of 10 minutes. After stirring the reaction mixture at room temperature for an additional 2 hours, the precipitate was collected and recrystallized from ethanol to give 250 mg of yellow crystals.

(*E*)-Methyl 3-(4-Pyridazinyl)-2-cyanoacrylate (**4**).

A solution of 324 mg (3 mmoles) of **1** and 297 mg (3 mmoles) of methyl cyanoacetate in 2 ml of dry methanol was stirred at room temperature for 5 hours. The precipitated solid was collected, washed with methanol and recrystallized from ethyl acetate-light petroleum to afford 360 mg of yellow crystals; ^{13}C nmr (deuteriodimethyl sulfoxide): δ 161.0 (C=O, $^3J_{CO/H-3}$ = 6.8 Hz), 152.1 (pyridazine C-6, $^1J_{CH}$ = 185.7 Hz), 150.0 (pyridazine C-3, $^1J_{CH}$ = 185.7 Hz, and olefinic C-3, $^1J_{CH}$ = 167.8 Hz), 129.5 (pyridazine C-4), 125.0 (pyridazine C-5, $^1J_{CH}$ = 171.2 Hz), 114.2 (C≡N, $^3J_{CN/H-3}$ = 14.0 Hz), 109.7 (olefinic C-2, $^2J_{C-2/H-3}$ = 1.7 Hz), 53.7 (OCH_3, $^1J_{CH}$ = 148.9 Hz).

Dimethyl (4-Pyridazinylmethylene)malonate (**5**).

A solution of 216 mg (2 mmoles) of **1**, 270 mg (2.04 mmoles) of dimethyl malonate, 13 mg of glacial acetic acid, and one drop of piperidine in 25 ml of toluene was refluxed for 20 hours using a water separator. After removal of the solvent, the resulting residue was subjected to column chromatography (dichloromethane-methanol, 29:1) to afford 107 mg (24%) of an analytically pure yellow oil which solidified with time. Recrystallization from diisopropyl ether gave yellow crystals.

(*E*)-Ethyl 3-(4-Pyridazinyl)acrylate (**6**).

A solution of 300 mg (2.78 mmoles) of **1** and 623 mg (2.78 mmoles) of triethyl phosphonoacetate in 5 ml of dry dimethyl formamide was treated with 83 mg (2.78 mmoles) of sodium hydride (80%-suspension in paraffine oil) and stirred at room temperature for 2 hours. After addition of 30 ml of water the reaction mixture was adjusted to *p*H 7 with 2*N* hydrochloric acid and extracted several times with dichloromethane. The combined organic layers were washed with water, dried over anhydrous sodium sulfate and evaporated. Column chromatography (dichloromethane-ethyl acetate, 1:2), followed by recrystallization from diisopropyl ether afforded 241 mg of pale yellow crystals.

2-(4-Pyridazinylmethylene)-1,3-indandione (**7**).

To a solution of 540 mg (5.0 mmoles) of **1** and 730 mg (5.0 mmoles) of 1,3-indandione in 20 ml of dichloromethane 3 drops of piperidine was added. The mixture was stirred for 8 hours at room temperature and then stored in the cold overnight. The precipitated solid was collected, washed with cold dichloromethane and recrystallized from ethanol to afford 830 mg of yellow crystals.

1-(4-Pyridazinyl)-2-nitro-1-propanol (**8**).

To a cooled (−20°) solution of 216 mg (2 mmoles) of **1** and 450 mg (6 mmoles) of nitroethane in 3 ml of ethanol two drops of diethylamine were added. The mixture was kept at −20° for 24 hours, then the precipitated solid was filtered off, washed with diethyl ether and recrystallized from ethanol to yield 320 mg of colorless crystals.

Reaction of 4-Pyridazinecarbaldehyde (**1**) with Nitromethane.

To a solution of 150 mg (1.39 mmoles) of **1** and 85 mg (1.39 mmoles) of nitromethane in 2 ml of dry methanol one drop of piperidine was added and the mixture was stirred at room temperature for 20 hours. After removal of methanol under reduced pressure, the residue was taken up in 10 ml of water and the resulting mixture was extracted several times with dichloromethane. The combined organic layers were dried and evaporated *in vacuo* to afford 20 mg of a residue, containing 90% of methyl 4-pyridazinecarboxylate (**11**), identical with an authentic sample [26], as shown by tlc and glc/ms. The aqueous layer was carefully evaporated under reduced pressure to give 85 mg of a residue, which turned out to contain 75% of methyl 4-pyridazinyl ketone (**12**) and 4% of **11**, again (according to glc/ms analysis) identical with authentic samples [27,26].

2,2'-(4-Pyridazinylmethylene)bis(1,3-indandione) (**10**).

To a solution of 108 mg (1 mmole) of **1** and 146 mg (1 mmole) of 1,3-indandione in 5 ml of 96% ethanol one drop of piperidine was added. The mixture was stirred for 8 hours at room temperature and was then stored in the cold overnight. The precipitated solid was collected, washed with cold ethanol and recrystallized from methanol to afford 166 mg of pink crystals.

Methyl 3-(3-Pyridazinyl)-2-cyanoacrylate (**13**).

To a solution of 159 mg (1.47 mmoles) of **2** and 146 mg (1.47 mmoles) of methyl cyanoacrylate in 2 ml of dry methanol one drop of triethylamine was added and the mixture was warmed to 50-60° for 30 seconds to start the reaction. After 2 hours standing at room temperature, the mixture was kept at 4° for additional 2 hours. The precipitate was filtered off, washed with methanol and recrystallized from methanol to afford 243 mg of yellow crystals.

Dimethyl (3-Pyridazinylmethylene)malonate (**14**).

To a solution of 324 mg (3 mmoles) of **2** and 396 mg (3 mmoles) of dimethyl malonate in 2 ml of dry dichloromethane 3 drops of diethylamine were added and the mixture was stirred for 10 hours at room temperature. Evaporation of the solvent gave a yellow oil, which was subjected to mplc (ethyl acetate-light petroleum, 1:1). Evaporation of the faster eluted fraction led to a solid which after recrystallization from ethyl acetate-light petroleum gave 200 mg of yellow crystals. The slower eluted fraction consisted of 100 mg of the starting aldehyde **2**.

Dimethyl [Hydroxy-(3-pyridazinyl)methyl]malonate (**15**).

To a solution of 324 mg (3 mmoles) of **2** and 396 mg (3 mmoles) of dimethyl malonate in 3 ml of dry methanol 3 drops of diethylamine was added at −10°. After stirring the mixture at this temperature for 5 hours, the precipitated solid was filtered off and recrystallized from ethyl acetate-light petroleum to afford 325 mg of colorless crystals.

(*E*)-3-(3-Pyridazinyl)acrylic Acid (**16**).

A mixture of 108 mg (1 mmole) of **2**, 104 mg (1 mmole) of malonic acid and 0.1 ml of dry pyridine was heated to 80° for 2 hours. After cooling, the reaction mixture was dissolved in 2*N* aqueous sodium hydroxide and treated with charcoal. After filtration, the remaining solution was adjusted to *p*H 2 with 2*N* hydrochloric acid and stored in the refrigerator. The precipitated crystals were collected, once again purified as described above and dried to give 40 mg of colorless prisms.

(*E*)-Ethyl 3-(3-Pyridazinyl)acrylate (**18**).

A solution of 300 mg (2.78 mmoles) of **2** and 623 mg (2.78 mmoles) of triethyl phosphonoacetate in 5 ml of dry dimethyl formamide was treated with 83 mg (2.78 mmoles) of sodium hydride (80% suspension in paraffine oil). The resulting mixture was stirred at 60° for 4 hours, cooled and poured into 30 ml of water. After extraction with dichloromethane, the combined organic layers were washed with water, dried and evaporated. Purification by mplc (dichloromethane-methanol, 7:3) afforded a low melting solid which after washing with diisopropyl ether gave 216 mg of nearly colorless crystals.

Dimethyl 2,4-Diacetyl-3-(4-pyridazinyl)glutarate (**19**).

A solution of 108 mg (1 mmole) of **1** and 116 mg (1 mmole) of methyl acetoacetate in 5 ml of methanol was refluxed for 10 hours. On cooling, a solid precipitated which was filtered off and recrystallized from methanol to afford 142 mg of colorless crystals.

General Procedure for the Preparation of 3,5-Symmetrically Substituted Dialkyl 2,6-Dimethyl-4-(4-pyridazinyl)-1,4-dihydropyridine-3,5-dicarboxylates **21a-c**, **23** and Dialkyl 2,6-Dimethyl-4-(3-pyridazinyl)-1,4-dihydropyridine-3,5-dicarboxylates **20a-c**.

A mixture of 3 mmoles of the pyridazinecarbaldehyde (for **20a-c**: 324 mg of **2**; for **21a-c**: 324 mg of **1**; for **23**: 366 mg of **22**), 6 mmoles of the corresponding alkyl acetoacetate (for **20a**, **21a**: 697 mg of methyl acetoacetate; for **20b**, **21b**, **23**: 781 mg of ethyl acetoacetate; for **20c**, **21c**: 865 mg of isopropyl acetoacetate), 1 ml of concentrated ammonia and 3 ml of methanol was refluxed for the appropriate time (for **20a**, **20b**, **21b**: 1 hour; for **20c**: 12 hours; for **21a**: 3 hours; for **21c**: 1.5 hours; for **23**: 13 hours). After cooling, the mixture was concentrated *in vacuo*, the precipitated solid was filtered off and recrystallized from the appropriate solvent.

Ethyl Methyl 2,6-Dimethyl-4-(3-pyridazinyl)-1,4-dihydropyridine-3,5-dicarboxylate (**20d**).

A solution of 324 mg (3 mmoles) of **2** and 348 mg (3 mmoles) of methyl acetoacetate in 4 ml of ethanol was refluxed for 10 minutes. Then a solution of 390 mg (3 mmoles) of ethyl 3-aminocrotonate in 10 ml of ethanol was added during a period of 2 hours and refluxing was continued for further 30 minutes. On cooling, a solid precipitated from the solution which was collected, washed with ethanol and recrystallized from ethanol-water to give 492 mg of pale yellow crystals.

Ethyl Methyl 2,6-Dimethyl-4-(4-pyridazinyl)-1,4-dihydropyridine-3,5-dicarboxylate (**21d**).

The preparation of compound **21d** from 324 mg (3 mmoles) of **1**, 348 mg (3 mmoles) of methyl acetoacetate, and 390 mg (3 mmoles) of ethyl 3-aminocrotonate was carried out in a similar manner as described for **20d**. Recrystallization from ethyl acetate-light petroleum afforded 377 mg of pale yellow needles.

Methyl *n*-Propyl 2,6-Dimethyl-4-(4-pyridazinyl)-1,4-dihydropyridine-3,5-dicarboxylate (**21e**).

A solution of 324 mg (3 mmoles) of **1**, 432 mg (3 mmoles) of *n*-propyl acetoacetate, and 345 mg (3 mmoles) of methyl 3-aminocrotonate in 3 ml of methanol was heated to reflux for 20 hours. After cooling, the precipitated solid was collected and recrystallized from methanol-water to afford 460 mg of pale yellow crystals.

Acknowledgements.

Support of this investigation by the "Fonds zur Förderung der wissenschaftlichen Forschung" (Projekt Nr. P6260C) and by the "Hochschuljubiläumsstiftung der Stadt Wien" is gratefully acknowledged. The authors are indebted to Mag. W. Trixner and Dr. A. Mayrhofer for synthetic contributions (compounds **8** and **16**) and to Mr. E. Möllner for recording ir spectra. C. Z. thanks the Republic of Austria for providing a grant (Nord-Süd Dialog Programm).

REFERENCES AND NOTES

[1] As Pyridazines **L** counts: G. Heinisch and T. Huber, *J. Heterocyclic Chem.*, **26**, 1787 (1989).

[2] Taken in part from the Ph.D. Thesis of W. Dostal, University of Vienna, Austria, 1987.

[3] Taken in part from the Diploma Thesis of I. Perhauc, University of Vienna, Austria, 1981.

[4] G. Heinisch and A. Mayrhofer, *Monatsh. Chem.*, **108**, 213 (1977).

[5] G. Heinisch, E. Luszczak and M. Pailer, *Monatsh. Chem.*, **104**, 1372 (1973).

[6] G. Heinisch and I. Kirchner, *J. Heterocyclic Chem.*, **17**, 1501 (1980).

[7] G. Heinisch, E. Luszczak and M. Pailer, *Monatsh. Chem.*, **105**, 763 (1974).

[8] The success of the procedure strongly depends on the precipitation of the condensation product from the reaction mixture. Otherwise the isolation of products becomes difficult and formation of considerable amounts of polymeric by-products takes place.

[9] Even in the absence of a basic catalyst formation of intractable tars is observed.

[10] Compound **16** has been prepared previously by condensation of 3-methylpyridazine with chloral followed by alkaline hydrolysis [11].

[11] R. G. Jones, E. C. Kornfeld and K. C. McLaughlin, *J. Am. Chem. Soc.*, **72**, 3539 (1950).

[12] G. Heinisch, A. Mayrhofer and R. Waglechner, *Arch. Pharm. (Weinheim)*, **315**, 175 (1982).

[13] K. Rehse and F. Brandt, *Arch. Pharm. (Weinheim)*, **317**, 54 (1984).

[14] It was tried to perform the reaction employing a variety of catalysts proposed for such purposes in the literature [15,16,17].

[15] E. Profft, F. Schneider and H. Beyer, *J. Prakt. Chem.*, **2**, 147 (1955).

[16] H. Meyer, F. Bossert, E. Wehinger, K. Stoepel and W. Vater, *Arzneim.-Forsch./Drug. Res.*, **31** (I), 407 (1981).

[17] W. Lehnert, *Tetrahedron*, **28**, 663 (1972).

[18] Due to the presence of several tautomeric forms in deuteriodimethylsulfoxide solution, we are not able to assign the signals in the ^{1}H-nmr spectrum of compound **19** unambigously.

[19] F. Bossert, H. Meyer and E. Wehinger, *Angew. Chem.*, **93**, 755 (1981); R. Mannhold, *Drugs of Today*, **20**, 69 (1984).

[20] F. Bossert and W. Vater, German Patent 2,005,116 (1971); *Chem. Abstr.*, **75**, 151687d (1971).

[21] H. Meyer, F. Bossert, W. Vater and K. Stoepel, German Patent 2,210,667 (1973); *Chem. Abstr.*, **79**, 146412p (1973).

[22] A. Vogt, K.-L. Neuhaus and H. Kreuzer, *Arzneim.-Forsch./Drug Res.*, **30** (II), 2162 (1980).

[23] P. B. Berntsson, S. A. I. Carlsson, J. O. Gaardner and B. R. Ljung, European Patent Appl. 7,293 (1980); *Chem. Abstr.*, **93**, 26283q (1980).

[24] H. H. Fox, J. I. Lewis and W. Wenner, *J. Org. Chem.*, **16**, 1259 (1951), and references cited therein.

[25] Since a similar ratio of products is observed when these reactions are performed in ethanol solution, transesterification of **21b** and **20b** can not provide a satisfactory explanation for the formation of the dimethylesters **21a** and **20a**.

[26] M. Robba, *Ann. Chim. (Paris)*, **5**, 351 (1960).

[27] G. Heinisch, *Monatsh. Chem.*, **104**, 953 (1973).