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PYRIDAZINES XXIV[1]

APPLICATION OF RADICALIC ETHOXYCARBONYLATION TO THE SYNTHESIS OF PYRIDAZINE MONO- AND POLYCARBOXYLIC ACID ESTERS

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Abstract - Reactivity of pyridazines 1, 2, 3, 16 towards ethoxycarbonylradical (generated by redox decomposition of oxyhydroperoxide of ethylpyruvate) was studied. Application of this type of homolytic substitution for synthesis of hitherto not accessible pyridazine carboxylic acid esters 6, 8, 9, 12, 13, 14, 15, 17 is demonstrated. In addition improved synthesis of diethyl 4,5-pyridazinedicarboxylate (5) is proposed.

Carbonation of 3-pyridazinyl lithium[2] so far represents the only method reported permitting C-C bond formation between the 1,2-diazine system and a carboxylic carbon atom. Considering earlier findings with radical alkylation[3,4], α-alkoxyalkylation[5], α-amidoalkylation[6] and acylation[7,8] of pyridazine derivatives, the experimentally simple procedure of homolytic alkoxycarbonylation now should allow introduction of COOR groups mainly into positions β to nitrogen atoms. In the field of pyridine and pyrimidine chemistry this type of Minisci reaction[9] has extensively been studied[10,11,12].

Our continuing interest in pyridazines and particularly in C-alkylpyridazines having functionalized carbon atoms directly attached to the heteroaromatic ring as starting materials for syntheses of compounds of potential pharmaceutical use, now prompted us to investigate reactivity of pyridazine (1), 3-methylpyridazine (2) and 4-methylpyridazine (3) towards ethoxycarbonylradical generated by redox decomposition[10] of oxyhydroperoxide of ethylpyruvate. The influence of various reaction conditions on product distribution was studied with the aim to find convenient pathways to hitherto not accessible mono- as well as polycarboxylated C-alkylpyridazines and also to diethyl 4,5-pyridazinedicarboxylate (5)[13,14].

RESULTS AND DISCUSSION

As shown in table 1 4-methylpyridazine (3) under standard conditions[10] (method A) yields three main products: Whereas structure of the mono- as well as the triethoxycarbonylated product unequivocally could be established as ethyl 5-methyl-4-pyridazinecarboxylate (9) and triethyl 5-methyl-3,4,6-pyridazinetricarboxylate (13) on basis of spectroscopic data (see experimental), two isomeric structures initially had to be taken into consideration for the diethyl 4-methylpyridazinedicarboxylate formed. However, it has to be formulated as diethyl 4-methyl-3,5-pyridazinedicarboxylate (12), as ethoxycarbonylation of ethyl 4-methyl-3-pyridazinecarboxylate (8)[15] yields the same product. Formation of 8 (obtained to a minor degree in reaction of 3) indicates that in spite of one β position still being unoccupied, attack of ethoxycarbonylradical surprisingly had taken place at C-3.

TABLE 1. Reactions of 4-Methylpyridazine (3) with Ethoxycarbonyl Radical

		% ratio of products (% yield[a])							
compound	reference	method A[b]		method B[c]		method C[d]		method D[e]	
3	30	20	/	65	/	-	/	31	/
8	-[f]	8	(11)	6	(17)	-	(-)	10	(14)
9	4	20	(26)	25	(72)	-	(-)	39	(56)
12	-	20	(26)	2	(6)	20	(20)	11	(16)
13	-	15	(19)	1	(3)	45	(45)	7	(10)
Σ N-COOEt compounds		9	(11)	-	(1)	13	(13)	-	(-)
Σ unidentified products		9	(11)	1	(3)	22	(22)	1	(3)

TABLE 2. Reactions of 3-Methylpyridazine (2) with Ethoxycarbonyl Radical

		% ratio of products (% yield[a])							
compound	reference	method A[b]		method B[c]		method C[d]		method D[e]	
2	32	21	/	69	/	-	/	29	/
10	-	1	(1)	8	(26)	-	(-)	2	(3)
11	25	-	(-)	4	(13)	-	(-)	1	(2)
14	-	30	(38)	19	(61)	30	(30)	67	(95)
15	-	20	(26)	-	(-)	29	(29)	-	(-)
Σ N-COOEt compounds		28	(36)	-	(-)	36	(36)	-	(-)
Σ unidentified products		-	(1)	-	(-)	5	(5)	-	(-)

TABLE 3. Reactions of Pyridazine (1) with Ethoxycarbonyl Radical

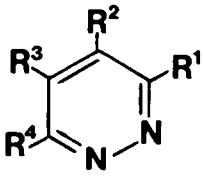
		% ratio of products (% yield[a])							
compound	reference	method A[b]		method B[c]		method C[d]		method D[e]	
1	33	10	/	51	/	-	/	14	/
4	31	2	(2)	19	(40)	-	(-)	13	(15)
5	13, 14	44	(49)	22	(45)	6	(6)	65	(76)
6	-	17	(19)	3	(7)	33	(33)	1	(1)
7	-[g]	1	(1)	-	(-)	6	(6)	-	(-)
Σ N-COOEt compounds		17	(19)	3	(5)	35	(35)	1	(1)
Σ unidentified products		9	(10)	3	(5)	20	(20)	7	(8)

TABLE 4. Reactions of 4-(2-Phenylethyl)-pyridazine (16) with Ethoxycarbonyl Radical

		% ratio of products (% yield[a])			
compound	reference	method A[b]		method D[e]	
16	34	33	/	11	/
17	-	23	(34)	70	(78)
18	-	10	(15)	1	(1)
19	-	7	(11)	-	(1)
20	-	1	(1)	-	(-)
Σ N-COOEt compounds		15	(22)	2	(2)
Σ unidentified products		9	(15)	16	(19)

a) yields based on converted base; b) base:peroxide ratio 1:3; c) base:peroxide ratio 3:1; d) base:peroxide ratio 1:10; e) base: peroxide ratio 1:3, reaction run in presence of CH_2Cl_2; f) 4-methyl-3-pyridazinecarboxylic acid see ref. 35; g) 3,4,5,6-pyridazinetetracarboxylic acid and tetramethyl 3,4,5,6-pyridazinetetracarboxylate see ref. 36, 37.

	R^1	R^2	R^3	R^4
1	H	H	H	H
2	CH_3	H	H	H
3	H	CH_3	H	H
4	H	$COOC_2H_5$	H	H
5	H	$COOC_2H_5$	$COOC_2H_5$	H
6	$COOC_2H_5$	$COOC_2H_5$	$COOC_2H_5$	H
7	$COOC_2H_5$	$COOC_2H_5$	$COOC_2H_5$	$COOC_2H_5$
8	$COOC_2H_5$	CH_3	H	H
9	H	$COOC_2H_5$	CH_3	H
10	CH_3	$COOC_2H_5$	H	H
11	CH_3	H	$COOC_2H_5$	H
12	$COOC_2H_5$	CH_3	$COOC_2H_5$	H
13	$COOC_2H_5$	$COOC_2H_5$	CH_3	$COOC_2H_5$
14	CH_3	$COOC_2H_5$	$COOC_2H_5$	H
15	$COOC_2H_5$	$COOC_2H_5$	$COOC_2H_5$	CH_3

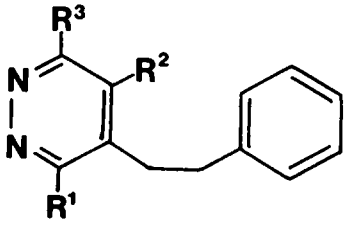


We now tried to minimize formation of polycarboxylated products from 3 by applying a base: peroxide ratio of 3:1 (method B). Under these conditions we did observe a drastical decrease of conversion rate but separation of 9, being the main product of the reaction, easily could be performed by column chromatography. Formation of 9 on homolytic methylation of ethyl 4-pyridazinecarboxylate (4) recently was reported[4], however, we had failed to separate 9 from other methylation products in a preparative scale.

Expecting that introduction of a COOR group into 3 should diminuish basicity of the heteroaromatic to such a degree that it is extractable quantitatively into organic solvents from an acidic aqueous layer, reaction of 3 with ethoxycarbonylradical in presence of dichloromethane (method D) was examined and indeed we obtained analytical pure 9 in about 40% yield (based on starting compound 3; i.e. 56% yield based on converted base). The advantage of this procedure on one hand results from suppression of further attack of radicals at 9 due to rapid transfer of the latter out of the aqueous reaction medium. On the other hand application of a base:peroxide ratio of 1:3 (like in method A) permits considerably higher conversion rate (about 70%) than that observed under conditions of method B.

Similar results were obtained in reactions of 4-(2-phenylethyl)-pyridazine 16 with ethoxycarbonylradical[16] (cf. table 4). Again method D provides a simple and most efficient tool to prepare a C-4 alkylated pyridazine bearing additionally one COOR group thus permitting synthesis of hitherto unknown 17[17] in 70% yield (based on starting 16[18]).

	R^1	R^2	R^3
16	H	H	H
17	H	$COOC_2H_5$	H
18	$COOC_2H_5$	$COOC_2H_5$	H
19	H	$COOC_2H_5$	$COOC_2H_5$
20	$COOC_2H_5$	$COOC_2H_5$	$COOC_2H_5$



The results of reactions of 3-methylpyridazine (2) and pyridazine (1) with ethoxycarbonyl radical under reaction conditions of methods A, B and D are summarized in tables 2 and 3. Due to both β positions free, the main products under conditions of method A are the diesters 14 and 5, respectively. Only traces of the monoesters (10, 11, 4) can be detected as obviously one introduced COOR group activates the 1,2-diazine system for attack of another radical. Accordingly, even in presence of an excess of the heteroaromatics (method B) the diesters 14 and 5 are dominating, methyl-pyridazinemonocarboxylic acid esters 10 and 11 are formed to a total amount of only 12%[19], 4 is obtained in 19% yield. Together with suppression of additional ethoxycarbonylation at α-carbon atoms, method B again is characterized by relatively low conversion rates (cf. tables 2,3).

On basis of these observations, together with findings with 4-methylpyridazine discussed above, convenient pathways to diethyl 4,5-pyridazinedicarboxylates were developed by reacting 2 or 1, respectively, under conditions of method D. Actually, this procedure represents an experimentally simple one step synthesis of 5[20] (obtained in 65% yield), starting with commercially available 1 as well as a high yield synthesis of hitherto unknown diethyl 3-methyl-4,5-pyridazinedicarboxylate (14).

The potential of Minisci type reactions performed in two-phase systems with respect to enhanced regioselectivity of radical attack at various π-deficient heteroaromatics at present is under investigation.

Formation of compounds 6, 7, 12, 13, 15, 18, 19, 20 in experiments with diazines 1, 2, 3, 16 under conditions of method A (cf. tables 1-4) gives evidence for ethoxycarbonyl radical also attacking positions α to nitrogen atoms at least if both β positions are occupied[21]. This prompted us to investigate reactions of 1, 2 and 3 applying base:peroxide ratios of 1:10 (method C) in order to prepare so far unknown pyridazinepolycarboxylic acid esters. As indicated by results listed in tables 1-3 there is a 100% conversion of starting materials and actually the triethyldiazine-tricarboxylates 6, 13, 15 are dominating the reaction mixtures[22].

Products of all experiments carried out easily could be separated by chromatography on silica gel or aluminium oxide. Compounds 4, 5, 9, 11, all known from literature (refs. see tables 1-4), were identified by comparison with authentic sample or by their ir, nmr and mass spectra. Structures of novel compounds 6, 7, 8, 10[19], 12, 13, 14, 15, 17, 18, 19, 20 were established by ms molecular weight determination, elemental analyses and spectroscopic data (see experimental).

Surprisingly, in reactions of 1, 2, 3 and 16, besides formation of some unidentified products, occurrence of 1-ethoxycarbonyl-1,2-dihydropyridazine derivatives was observed. It is of interest to note that attack of a carbon radical to the nitrogen atom of a π-electron deficient heteroaromatic under conditions of Minisci reaction is without precedence. Structures and reactivities of these novel compounds at present are under investigation.

The results obtained in this study continue to demonstrate the versatility of homolytic substitution reactions with respect to preparation of so far not accessible pyridazine derivatives as well as to improved synthesis of important building blocks which hitherto only were available by multi step procedures.

EXPERIMENTAL

Melting points (uncorrected) were determined with a Kofler apparatus. Ir spectra were recorded on a Jasco IRA-1 spectrometer (KBr disks; $\tilde{\nu}$ in cm^{-1}). ^{1}H-nmr spectra were recorded with a Varian EM 390 (90 MHz), using $CDCl_3$ as solvent; chemical shifts (J in Hz) are reported in ppm downfield from internal TMS. Mass spectra were obtained on a Varian MAT CH-7. Microanalyses were performed by the Institut für Physikalische Chemie (University of Vienna, Dr. Zak). Glc analyses were carried out with a Varian VAE 1400 or a Varian 2700 (N_2, 30ml/min; FID); 2 m x 6.35mm glass columns, packed with 3% OV 17 on Chromosorb WAW (for reaction mixtures of 1, 3, 16) or 3% OV 101 on Chromosorb WAW (for reaction mixtures of 2), respectively, were used. Medium pressure liquid chromatography (mplc) was carried out in glass columns (Ø= 36mm, l= 550mm), filled with 250g Li-Chroprep® Si 60 (40-63 µm, Merck), flow rate 10ml/min. Preparative thin layer chromatography (prep. tlc) was carried out on aluminium oxide plates F-254 (Type T, Merck).

All reagents were commercial products and were reacted without further purification. 1, 2, 3[30] were distilled before use.

General Procedure for the Reaction of Pyridazines 1, 2, 3, 16 with Ethoxycarbonyl Radical

Method A. Under stirring and cooling (-10° - 0°) a 30% aqu. solution of H_2O_2 (3.4g, 0.03mol) is added dropwise to ethylpyruvate (5.2g, 0.045mol) and stirring at -10° - 0° is continued for 15min. This solution is added dropwise at -5° - 0° to a stirred mixture of the heteroaromatic (0.01mol), $FeSO_4.7H_2O$ (6.8g, 0.03mol), H_2SO_4 conc. (3g, 0.03mol) and water (4ml). Stirring is continued for another 15min, then the reaction mixture is poured into ice water and extracted with CH_2Cl_2. The organic layer is washed with water and dried over Na_2SO_4. The solvent and excess ethylpyruvate is removed in vacuo, the remaining yellow oils are separated by mplc or prep. tlc. Unconverted starting compounds 1, 2, 3 are recovered after basifying the aqueous layers with NH_4OH conc. by extraction with CH_2Cl_2 .

Methods B,C. The reactions are carried out as outlined above employing a base:peroxide ratio of 3:1 (method B) or 1:10 (method C), respectively.

Method D. A base:peroxide ratio of 1:3 is employed, the reactions are run in similar manner by dropping the solution of oxyhydroperoxide of ethylpyruvate at -5° - 0° into a well stirred mixture of 30ml CH_2Cl_2 and the acidic aqueous solution, containing the heteroaromatic and $FeSO_4.7H_2O$.

Ethyl 4-pyridazinecarboxylate (4)[31]. Separation by mplc (dichloromethane/ethyl acetate 5/1), analytic sample by distillation (76°, 1mbar).

Diethyl 4,5-pyridazinedicarboxylate (5)[13,14]. Separation by mplc (dichloromethane/ethyl acetate 5/1), analytic sample by kugelrohr distillation (130°, 10^{-1} mbar).

Triethyl 3,4,5-pyridazinetricarboxylate (6). Separation by mplc (dichloromethane/ethyl acetate 5/1), analytic sample by kugelrohr distillation (150°, 10^{-1}mbar), yellow crystals, mp <30°; ms: M^+ at m/e 296, major peaks at 252, 223, 152 (100%); ir: 1732 ($\nu_{C=O}$); nmr: 9.82 (s, 1H, H-6), 4.74-4.33 (m, 6H, 3x CH_2), 1.65-1.23 (m, 9H, 3x CH_3); Anal. calcd. for $C_{13}H_{16}N_2O_6$: C, 52.70; H, 5.44; N, 9.46; Found: C, 52.85; H, 5.60; N, 9.11.

Tetraethyl 3,4,5,6-pyridazinetetracarboxylate (7). Separation and analytic sample by mplc (dichloromethane/ethyl acetate8/1), yellow crystals, mp <30°; ms: M^+ at m/e 368, major peaks at 324 (100%), 295; ir: 1745 ($\nu_{C=O}$); nmr: 4.72-4.20 (m, 8H, 4x CH_2), 1.62-1.15 (m, 12H, 4x CH_3); Anal. calcd. for $C_{16}H_{20}N_2O_8$: C, 52.17; H, 5.47; N, 7.61; Found: C, 52.08; H, 5.61; N, 7.24.

Ethyl 4-methyl-3-pyridazinecarboxylate (8). Separation by mplc (dichloromethane/ethyl acetate 10/1), analytic sample by recrystallisation from diethylether, white crystals, mp 75°-80°; ms: M^+ at m/e 166, major peaks at 122, 94 (100%), 67; ir: 1720 ($\nu_{C=O}$); nmr: 9.15 (d, J=5, 1H, H-6), 7.44 (d, J=5, 1H, H-5), 4.52 (q, J=7, 2H, CH_2), 2.59 (s, 3H, C-4-CH_3), 1.50 (t, J=7, $CH_2\underline{CH_3}$); Anal. calcd. for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86; Found: C, 57.62; H, 6.07; N, 16.67.

Ethyl 5-methyl-4-pyridazinecarboxylate (9). Separation and analytic sample by mplc (dichloromethane/ethyl acetate 10/1), yellow crystals, mp <30°; ms: M^+ at m/e 166 (100%), major peaks at 138, 121, 65; ir: 1722 ($\nu_{C=O}$); nmr: cf. ref. 4; Anal. calcd for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86; Found: C, 57.89; H, 6.12; N, 16.62.

Ethyl 3-methyl-4-pyridazinecarboxylate (10) and Ethyl 3-methyl-5-pyridazinecarboxylate (11)[25]. Separation of 10 + 11 mixture (containing 66% 10 and 33% 11) from other reaction products by mplc (dichloromethane/ethyl acetate 3/1). ^{1}H-nmr: besides signals of 11[25]: 9.30 (d, J=6, 1H, H-6), 7.8 (d, J=6, 1H, H-5) (overlapping with H-4 signal of 11), 4.4 (q, J=7, 2H, CH_2) (overlapping with CH_2 signal of 11), 3.00 (s, 3H, CH_3), 1.41 (t, J=7, 3H, CH_2-$\underline{CH_3}$) (collapsing with CH_2-$\underline{CH_3}$ signal of 11)

Diethyl 4-methyl-3,5-pyridazinedicarboxylate (12). Separation by mplc (dichloromethane/ethyl acetate 10/1), analytic sample by kugelrohr distillation (160°, 10^{-1}mbar), yellow oil; ms: M^+ at m/e 238, major peaks at 193, 166 (100%), 138; ir: 1720 ($\nu_{C=O}$); nmr: 9.50 (s, 1H, H-6), 4.74-4.32 (m, 4H, 2x CH_2), 2.70 (s, 3H, C-4-CH_3), 1.64-1.31 (m, 6H, 2x CH_2-$\underline{CH_3}$); Anal. calcd. for $C_{11}H_{14}N_2O_4$: C, 55.46; H, 5.92; N, 11.76; Found: C, 55.22; H, 5.90; N, 11.65.

Triethyl 5-methyl-3,4,6-pyridazinetricarboxylate (13). Separation by mplc (dichloromethane/ethyl acetate 10/1), analytic sample by kugelrohr distillation (190°, 10^{-1}mbar), yellow oil; ms: M^+ at m/e 310, major peaks at 265, 238, 166 (100%), 137, 94; ir: 1735 ($\nu_{C=O}$); nmr: 4.74-4.29 (m, 6H, 3x CH_2), 2.51 (s, 3H, C-5-CH_3), 1.62-1.22 (m, 9H, 3x CH_2-$\underline{CH_3}$); Anal. calcd. for $C_{14}H_{18}N_2O_6$: C, 54.19; H, 5.84; N, 9.03; Found: C, 54.03; H, 5.78; N, 8.92.

Diethyl 3-methyl-4,5-pyridazinedicarboxylate (14). Separation by mplc (dichloromethane/ethyl acetate 5/1), analytic sample by prep. tlc on aluminium oxide (dichloromethane/ethyl acetate 3/1), yellow oil; ir: 1735 ($\nu_{C=O}$); nmr: 9.60 (s, 1H, H-6), 4.68-4.30 (m, 4H, 2x CH_2), 2.82 (s, 3H, C-3-CH_3), 1.58-1.21 (m, 6H, 2x CH_2-$\underline{CH_3}$); hrms calcd. for $C_{11}H_{14}N_2O_4$: 238.095(4); Found: 238.095(8) ± 0.0012.

Triethyl 6-methyl-3,4,5-pyridazinetricarboxylate (15). Separation and analytic sample by mplc (dichloromethane/ethyl acetate 5/1), yellow crystals, mp <30°; ms: M^+ at m/e 310, major peaks at 266, 237 (100%), 209, 166, 165, 94, 91; ir: 1740 ($\nu_{C=O}$); nmr: 4.70-4.27 (m, 6H, 3x CH_2), 2.91 (s, 3H, C-6-CH_3), 1.60-1.20 (m, 9H, CH_2-CH_3); Anal. calcd for $C_{14}H_{18}N_2O_6$: C, 54.19; H, 5.84; N, 9.03. Found: C, 53.95; H, 5.80; N, 8.89.

Ethyl 5-(2-phenylethyl)-4-pyridazinecarboxylate (17). Separation by mplc (dichloromethane/ethyl acetate 8/1), analytic sample by recrystallisation from toluene/petroleum benzine (50°-70°), pale yellow crystals, mp 77°-82°; (Extraction of 17 in a preparative scale is accomplished by removal of the solvent and excess ethylpyruvate in vacuo, followed by simply filtering the resulting yellow oil obtained through silica gel and subsequent crystallisation.) ms: M^+ at m/e 256, major peaks at 227, 184, 91 (100%); ir: 1720 ($\nu_{C=O}$); nmr: 9.54 (s, 1H, H-3), 9.13 (s, 1H, H-6), 7.48-7.05 (m, 5H, phenyl-H), 4.47 (q, J=7, 2H, CH_2-CH_3), 3.48-2.81 (m, 4H, CH_2-CH_2), 1.45 (t, J=7, 3H, CH_2-CH_3); Anal. calcd. for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93; Found: C, 70.27; H, 6.35; N, 11.11.

Diethyl 4-(2-phenylethyl)-3,5-pyridazinedicarboxylate (18)[38]. Separation by mplc (dichloromethane/ethyl acetate 8/1), analytic sample by recrystallisation from petroleum benzine (50°-70°), pale yellow crystals, mp 79°-85°; ms: M^+ at m/e 328, major peaks at 299, 253, 91 (100%); ir: 1740 ($\nu_{C=O}$), 1730 ($\nu_{C=O}$); nmr: 9.52 (s, 1H, H-6), 7.40-7.16 (m, 5H, phenyl-H), 4.70-4.30 (m, 4H, 2x CH_2-CH_3), 3.58-3.32, 3.19-2.83 (2x m, 4H, CH_2-CH_2), 1.62-1.31 (m, 6H, 2x CH_2-CH_3); Anal. calcd. for $C_{18}H_{20}N_2O_4$: C, 65.84; H, 6.14, N, 8.53; Found: C, 65.70; H, 6.25; N, 8.59.

Diethyl 5-(2-phenylethyl)-3,4-pyridazinedicarboxylate (19)[38]. Separation by mplc (dichloromethane/ethyl acetate 8/1), analytic sample by prep. tlc on aluminium oxide (dichloromethane/ethyl acetate 8/1), yellow oil; ir: 1730 ($\nu_{C=O}$); nmr: 9.10 (s, 1H, H-6), 7.48-7.07 (m, 5H, phenyl-H), 4.70-4.29 (m, 4H, 2x CH_2-CH_3), 3.12-2.93 (m, 4H, CH_2-CH_2), 1.60-1.18 (m, 6H, 2x CH_2-CH_3); hrms calcd. for $C_{18}H_{20}N_2O_4$: 328.142(3); Found: 328.144(4) ± 0.003.

Triethyl 5-(2-phenylethyl)-3,4,6-pyridazinetricarboxylate (20). Separation by mplc (dichloromethane/ethyl acetate 5/1), analytic sample by mplc (dichloromethane/ethyl acetate 8/1), yellow crystals, mp <30°; ms: M^+ at m/e 400, major peaks at 354, 325, 91 (100%); ir: 1740 ($\nu_{C=O}$); nmr: 7.42-7.19 (m, 5H, phenyl-H), 4.70-4.33 (m, 6H, 3x CH_2-CH_3), 3.21-2.79 (m, 4H, CH_2-CH_2), 1.62-1.25 (m, 9H, 3x CH_2-CH_3); Anal. calcd. for $C_{21}H_{24}N_2O_6$: C, 62.99; H, 6.04; N, 7.00; Found: C, 62.89; H, 6.04; N, 7.15.

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15) 8 was reacted with ethoxycarbonyl radical under conditions of method A. The ^{1}H-nmr spectrum of the reaction mixture obtained, in addition to signals of 8 and minor amounts of unidentified by-products, exhibits signals at 9.50 ppm and 2.70 ppm (compare with data of compound 12).
16) Ethyl 5-styryl-4-pyridazinecarboxylate[4] on attempted catalytic hydrogenation (Pd/C) instead of 17 yielded a complex reaction mixture.
17) Intramolecular ring closure reactions starting with 17 as well as with ethyl 5-styryl-4-pyridazinecarboxylates[4] according to methods used by different authors for preparation of monoaza-dibenzocycloheptadiene or -triene system[23,24] at present are examined.

18) Whereas in reactions of compounds 1, 2, 3 (see tables 1-3) under conditions of method D conversion rates are slightly lower than those observed when applying method A, in reactions of 16 they markedly are increasing by changing from method A to method D, obviously due to solubility reasons.
19) Attempts to separate 10 from 11 by glc failed. However, due to the fact that 11 is a known compound[25], ^{1}H-nmr spectrum of the 10 + 11 mixture permits estimation of 10:11 ratio (2:1) as well as unambigous structure determination of novel compound 10.
20) So far 5, being an important starting material for preparation of e.g. pyridazino [4,5-d] pyridazines[14], pyridazino[4,5-c]-[1,6] benzodiazocines[26] and diaza-spirodecadienes[27,28], has been prepared by esterification[14] of 4,5-pyridazinedicarboxylic acid, only available by multi step processes[29].
21) Radical attack at C-3 and/or C-6 has been observed in reactions of pyridazine derivatives with 1,3,5-trioxanyl- as well as methyl radical[4,5]. In contrast, homolytic acylation[7,8] takes place exclusively at C-4 and/or C-5.
22) Only small amounts of tetraethyl 3,4,5,6-pyridazinetetracarboxylate are formed, probably due to enhanced formation of by-products, some of which could be identified as 1-ethoxycarbonyl-1,2-dihydropyridazine derivatives.
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38) Differentiation between 18 and 19 is based on chemical shifts of H-3 and H-6 protons, respectively, according to $\Delta\delta$ in ^{1}H-nmr spectra of 10 and 11.