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PYRIDAZINES-XXXIX[1]
N-SUBSTITUTED 1,2-DIHYDRO-1,2-DIAZINES FORMED IN HOMOLYTIC ALKOXYCARBONYLATION REACTIONS OF PYRIDAZINES

Martina Gebauer[2], Gottfried Heinisch* and Gerhard Lötsch

Institut für Pharmazeutische Chemie, Universität Wien
Währingerstraße 10
A-1090 Wien, Österreich

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Abstract: Pyridazine and C-alkylpyridazines were found to yield N-ethoxycarbonyl-1,2-dihydropyridazines 1 - 6 when subjected to conditions of homolytic ethoxycarbonylation. This is the first example of an attack of a radical at the nitrogen atom of a N-heteroarene in *Minisci*-type reactions.

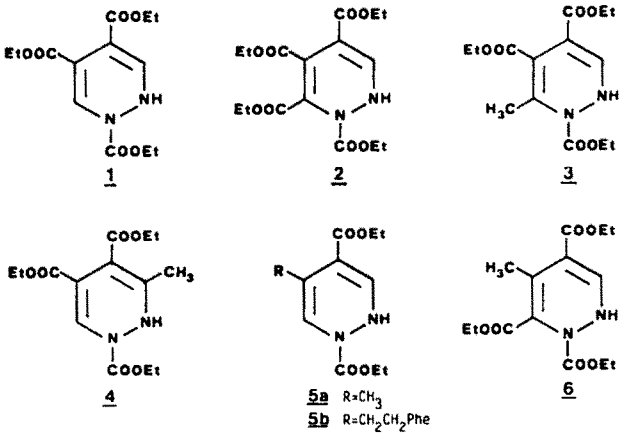
Substitution reactions employing nucleophilic carbon-centered free radicals are versatile tools for the introduction of alkyl, acyl, aroyl, α-alkoxyalkyl and α-N-amidoalkyl groups into the protonated pyridazine system[3]. In the course of an investigation[4] directed to the synthesis of alkyl pyridazinecarboxylates by means of *Minisci*-type reactions[5] we recently observed (besides formation of the expected C_4-carboxylated products) occurrence of compounds, which surprisingly proved to be N-alkoxycarbonyl-dihydropyridazine derivatives.

We here report on the determination of the structures of these novel compounds isolated in up to 36% yield (cf. table 1) after mplc separation of the mixtures obtained in homolytic ethoxycarbonylation reactions. Moreover, a plausible mechanistic interpretation of the formation of N-substituted dihydroheteroarenes in *Minisci*-reactions, which to our knowledge is unprecedented, is discussed.

Elemental analyses, ms molecular weight determinations and $\nu_{(C=O)}$ absorption bands between 1745 and 1707cm^{-1} as well as between 1690 and 1640cm^{-1} clearly indicate the products, which exhibit striking fluorescence (on irradiation with UV_{366nm}), to be N-ethoxycarbonyl-dihydropyridazinecarboxylic acid esters. In addition, N-H stretching vibrations at ~3000cm^{-1} in the ir spectra and broadened one-proton signals in the ^{1}H-nmr spectra (slowly disappearing after D_2O addition) permit to exclude other structures than those of 1,2-dihydropyridazine derivatives. The positions of substituents in compounds 1 - 4 could be determined by means of ^{1}H-nmr spectroscopy. According to the spectral data structures 1 and 2 have to be assigned to the N-ethoxycarbonyl compounds obtained from the parent heterocycle. Also the two tricarboxylates resulting from reaction of 3-methylpyridazine with ethoxycarbonyl radicals easily can be discriminated, since the ^{1}H-nmr spectrum of 3 shows NH-CH coupling (J=4Hz), whereas in the spectrum of compound 4 the one-proton signal at 6.82ppm appears as a singlet.

Table 1. Yields of 1-ethoxycarbonyl-1,2-dihydropyridazine derivatives
(based on starting heteroaromatic substrate)

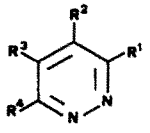
Starting compound	base:peroxide=1:3	base:peroxide=1:10
pyridazine	1 (17%) 2 (<1%)	1 (35%) 2 (1%)
3-methylpyridazine	3 (12%) 4 (16%)	3 (18%) 4 (18%)
4-methylpyridazine	5a(6%) 6 (3%)	5a(6%) 6 (7%)
4-(2-phenylethyl)-pyridazine	5b(15%)	--
ethyl 4-pyridazinecarboxylate	1 (36%) 2 (<1%)	--
diethyl 4,5-pyridazine-dicarboxylate (7g)	1 (24%) 2 (<1%)	--



Also in the tricarboxylate derived from 4-methylpyridazine the signal of the olefinic proton is split into a doublet. This, however, does not permit an unequivocal structure proof, since triethyl 5-methyl-1,4,6-(1,2-dihydropyridazine)tricarboxylate as well as triethyl 4-methyl-1,5,6-(1,2-dihydropyridazine)tricarboxylate have to be taken into consideration. But assignment of structure 6 unambigously could be achieved by an additional experiment: diethyl 4-methyl-3,5-pyridazinedicarboxylate[4] (7e) yielded an identical product upon homolytic ethoxycarbonylation.

Besides compound 6, the reaction of 4-methylpyridazine afforded a C,N-dicarboxylate, the ^{1}H-nmr spectrum of which exhibits two signals within the observed range of protons α to nitrogen atoms in N-ethoxycarbonylated 1,2-dihydropyridazines (doublet at 7.44ppm, singulet at 6.52ppm). Again, these data alone do not permit to draw definitive conclusions regarding the position of the N-COOEt moiety relative to the alkyl substituent. Ring-H / methyl-H coupling could not be observed, we also failed in attempts to elucidate the substitution pattern by n.o.e. experiments. Neither did ^{13}C-nmr spectroscopy provide sufficient information.
As illustrated in table 2 the replacement of a COOEt moiety attached to a ring carbon-atom in N-ethoxycarbonyl-1,2-dihydropyridazinetricarboxylic acid ester 8a (=2) by a methyl group causes an upfield shift of the olefinic proton signal, the

magnitude of which decreases with increasing number of bonds between this proton and the alkyl substituent. A similar phenomenon is observed with H_α in pyridazinecarboxylic acid esters 7a-h. Considering that in the C,N-dicarboxylate obtained from 4-methylpyridazine the olefinic proton singulet is shifted upfield to a larger extent than the doublet of the second olefinic proton in comparison to H-3 and H-6 of compound 8d (=1) (see table 2), one may assume the methyl group to be attached to ring carbon-atom 5 rather than to C-4. Thus, assignment of structure 5a (=8f) to the novel compound appears to be reasonable. Similar considerations prompt us to propose structure 5b (=8h) for the C,N-dicarboxylate obtained from 4-(2-phenylethyl)pyridazine.



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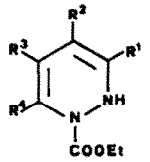
	R^1	R^2	R^3	R^4
7a	COOEt	COOEt	COOEt	H
7b	COOEt	COOEt	CH_2CH_2Phe	H
7c	COOEt	CH_2CH_2Phe	COOEt	H
7d	COOEt	COOEt	CH_3	H
7e	COOEt	CH_3	COOEt	H
7f	CH_3	COOEt	COOEt	H
7g	H	COOEt	COOEt	H
7h	H	COOEt	CH_3	H



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8a(=2)	H	COOEt	COOEt	COOEt
8b(=6)	H	COOEt	CH_3	COOEt
8c(=3)	H	COOEt	COOEt	CH_3
8d(=1)	H	COOEt	COOEt	H
8e	H	CH_3	COOEt	H
8f(=5a)	H	COOEt	CH_3	H
8g	H	CH_2CH_2Phe	COOEt	H
8h(=5b)	H	COOEt	CH_2CH_2Phe	H

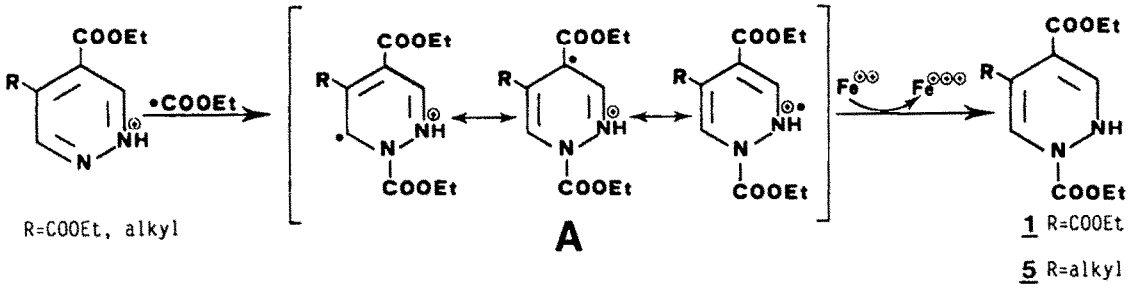
Table 2. Chemical shifts of Hα in pyridazinecarboxylic acid esters[4,6] and 1,2-dihydropyridazinecarboxylic acid esters

	δH_α (=R^1)	$\delta H_\alpha'$ (=R^4)
7a	---	9.82
7b	---	9.10
7c	---	9.52
7d	---	9.30
7e	---	9.50
7f	---	9.60
7g	9.57	9.57
7h	9.44	9.18
8a(=2)	7.67	---
8b(=6)	7.45	---
8c(=3)	7.62	---
8d(=1)	7.62	6.84
8f(=5a)	7.44	6.52
8h(=5b)	7.52	6.51

Δδ=-0.72; Δδ=-0.30; Δδ=-0.52; Δδ=-0.32; Δδ=-0.22; Δδ=-0.13; Δδ=-0.39; Δδ=-0.22; Δδ=-0.05; Δδ=-0.18; Δδ=-0.10; Δδ=-0.32; Δδ=-0.33

In order to obtain insight into the mechanism which accounts for the occurence of these unusual reaction products, homolytic ethoxycarbonylation reactions employing ethyl 4-pyridazinecarboxylate, diethyl 4,5-pyridazinedicarboxylate (7g) and ethyl 5-methyl-4-pyridazinecarboxylate (7h) were investigated. N-carboxylates 1 and 2 as well as 5 and 6 (thus being products identical with those obtained from pyridazine or 4-methylpyridazine, respectively) were found to be formed in these reactions under standard conditions[4], i.e. in the absence of an organic layer.

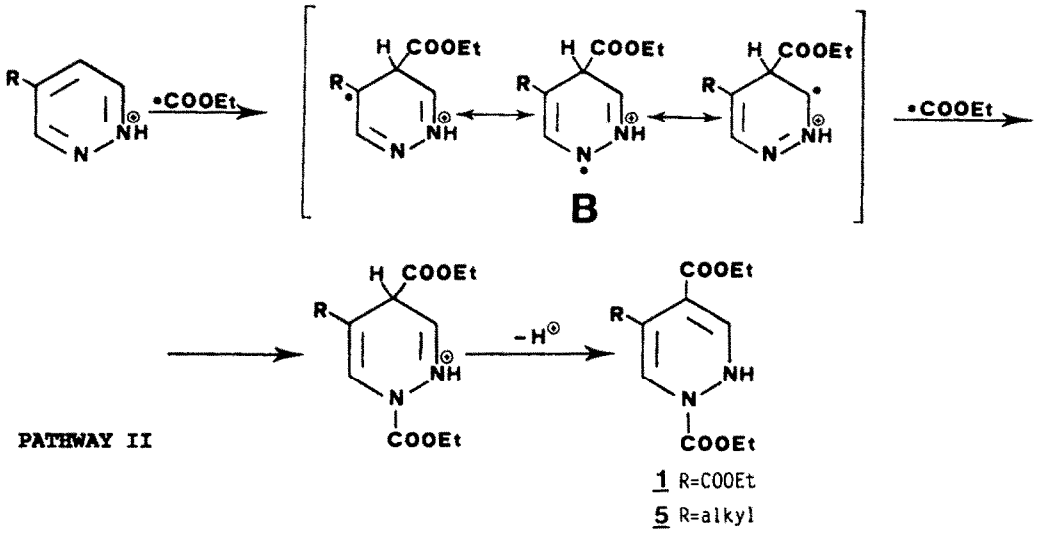
Accordingly, when 7g and 7h are considered to be intermediates in the formation of the above mentioned N-carboxylates, one might propose pathway I displayed below, which is characterised by attack of the radical at the non-protonated nitrogen-atom of the 1,2-diazine system.



PATHWAY I

In a similar manner pathway I may account for the formation of compounds 2 and 6, since 6 also was obtained when 7e was used as the educt. In this context it has to be referred to the report by *Minisci* and co-workers on reactions of diazonium salts with nucleophilic carbon-centered radicals[7].

Of course, formation of N-carboxylates 1 and 5 from the parent heterocycle or its 4-methyl derivative also could take place according to pathway II via interaction of two radicals (the COOEt radical and radical B).



PATHWAY II

However, this mechanism does not permit to explain that compounds 1 and 5 also are obtained, when 7g or 7h are subjected to the homolytic alkoxycarbonylation reaction and that compounds 2 and 6 are formed from 7a or 7e, respectively. Neither can pathway II provide a reasonable explanation for the results of ethoxycarbonylation experiments with pyridazine and 4-methylpyridazine in the presence of dichloromethane[4]. Under these conditions, which enable us to prepare 4,5-disubstituted pyridazines in high yield by avoiding additional radicalic attack at ring carbon-atoms, only traces (<1%) of N-ethoxycarbonylated products are formed[4].

Finally, it should be noted that the electronic properties of an alkyl and an alkoxycarbonyl substituent call for assuming protonation of N-1 in 4-methylpyridazine and of N-2 in ethyl 5-methyl-4-pyridazinecarboxylate (7h) thus permitting to exclude other pathways than those discussed above. This is supported by the fact that only compound 5a but not its isomer 8e is formed from 4-methylpyridazine.

EXPERIMENTAL

The homolytic ethoxycarbonylation reactions were performed as described in ref.[4] applying base:peroxide ratios of 1:3 (method A) and 1:10 (method C). For yields see table 1.

Melting points (uncorrected) were determined with a Kofler apparatus. Ir spectra were recorded on a Jasco IRA-1 spectrometer (KBr disks, unless otherwise noted; ν in cm^{-1}). ^1H-nmr spectra were recorded with a Varian EM 390 (90MHz), using $CDCl_3$ as solvent; chemical shifts (J in Hz) are reported in ppm downfield from internal TMS. Mass spectra were obtained on a Finnigan MAT 311A and on a Hewlett Packard 5970B-MSD. Microanalyses were performed by the Institut für Physikalische Chemie (University of Vienna, Dr.Zak). Glc analyses were carried out with a Hewlett Packard 5890A/ 5970B-MSD, using a 12m HP1-FS-WCOT column. Medium pressure liquid chromatography (mplc) was carried out in Lobar® glass columns filled with 250g LiChroprep® Si 60 (Merck). Preparative thin layer chromatography (prep. tlc) was carried out on aluminium oxide plates (type T, Merck).

Triethyl 1,4,5-(1,2-dihydropyridazine)tricarboxylate (1). Separation by mplc of a reaction mixture obtained from pyridazine (dichloromethane/ethyl acetate 5/1), analytic sample by kugelrohr distillation (180°C,10^{-1}mbar), yellow crystals, mp <25°C; ms: M^+ at m/e 298, major peaks at 225 (100%), 125, 80; ir: 3120 (ν_{N-H}), 1745, 1727, 1672 ($\nu_{C=O}$); nmr: 8.99 (d, J=4, 1H, H-2, exchangeable with D_2O), 7.62 (d, J=4, 1H, H-3, s after D_2O exchange), 6.84 (s, 1H, H-6), 4.46-4.03 (m, 6H, 3x CH_2), 1.48-1.10 (m, 9H, 3x CH_3); Anal. calcd. for $C_{13}H_{18}N_2O_6$: C, 52.34; H, 6.08; N, 9.39. Found: C, 52.67; H, 6.18; N, 9.49.

Tetraethyl 1,4,5,6-(1,2-dihydropyridazine)tetracarboxylate (2). Separation by mplc of a reaction mixture obtained from pyridazine (dichloromethane/ethyl acetate 5/1), analytic sample after mplc (dichloromethane/ethyl acetate 8/1), yellow crystals, mp <25°C; ms: M^+ at m/e 370, major peak at 297 (100%); ir 3080 (ν_{N-H}), 1728, 1640 ($\nu_{C=O}$); nmr: 9.67 (d, J=4, 1H, H-2, exchangeable with D_2O), 7.67 (d, 1H, J=4, H-3, s after D_2O exchange), 4.50-4.06 (m, 8H, 4x CH_2), 1.53-1.12 (m, 12H, 4x CH_3); Anal. calcd. for $C_{16}H_{22}N_2O_8$: C, 51.89; H, 5.99; N, 7.56. Found: C, 51.90; H, 6.11; N, 7.20.

Triethyl 6-methyl-1,4,5-(1,2-dihydropyridazine)tricarboxylate (3).Separation by mplc of a reaction mixture obtained from 3-methylpyridazine (dichloromethane/ethyl acetate 5/1), analytic sample after preparative tlc on aluminium oxide (dichloromethane/ethyl acetate 3/1), colourless crystals, mp=62-66°C; ms: M^+ at m/e 312, major peaks at 239 (100%), 211, 139; ir: 3120 (ν_{N-H}), 1730, 1723, 1670 ($\nu_{C=O}$); nmr: 8.13 (d, J=4, 1H, H-2, exchangeable with D_2O), 7.62 (d, J=4, 1H, H-3, s after D_2O exchange), 4.43-4.06 (m, 6H, 3x CH_2), 2.19 (s, 3H, C-6-CH_3), 1.43-1.13 (m, 9H, 3x CH_2-$\underline{CH_3}$); Anal. calcd. for $C_{14}H_{20}N_2O_6$: C, 53.84; H, 6.46; N, 8.97. Found: C, 53.66; H, 6.40; N, 8.67.

Triethyl 3-methyl-1,4,5-(1,2-dihydropyridazine)tricarboxylate (4). Separation by mplc of a reaction mixture obtained from 3-methylpyridazine (dichloromethane/ethyl acetate 5/1), analytic sample after kugelrohr distillation (75°C, 10^{-1}mbar), yellow crystals, mp=99-101°C; ms: M^+ at m/e 312, major peaks at 239 (100%), 237, 211, 139, 94; ir: 3110 (ν_{N-H}), 1738, 1654 ($\nu_{C=O}$); nmr: 7.72 (s, 1H, H-2, exchangeable with D_2O), 6.82 (s, 1H, H-6) 4.40-4.01 (m, 6H, 3x CH_2), 2.32 (s, 3H, C-3-CH_3), 1.42-1.10 (m, 9H, 3x CH_2-$\underline{CH_3}$). Anal. calcd. for $C_{14}H_{20}N_2O_6$: C, 53.84; H, 6.45; N, 8.97. Found: C, 54.14; H, 6.41; N, 8.78.

Diethyl 5-methyl-1,4-(1,2-dihydropyridazine)dicarboxylate (5a). Separation by mplc of a reaction mixture obtained from 4-methylpyridazine (dichloromethane/ethyl acetate 10/1), analytic sample after mplc (dichloromethane/ethyl acetate 5/1), yellow crystals, mp <25°C; ms: M^+ at m/e 240, major peaks at 167 (100%), 139, 121; ir: 3110 (ν_{N-H}), 1735, 1728, 1688 ($\nu_{C=O}$); nmr: 8.32 (d, J=4, 1H, H-2, exchangeable with D_2O), 7.44 (d, J=4, 1H, H-3, s after D_2O exchange), 6.52 (s, 1H, H-6), 4.40-4.03 (m, 4H, 2x CH_2), 1.48 (s, 3H, C-5-CH_3), 1.39-1.13 (m, 6H, 2x CH_2-$\underline{CH_3}$); Anal. calcd. for $C_{11}H_{16}N_2O_4$: C, 54.99; H, 6.71; N, 11.66. Found: C, 55.09; H, 6.72; N, 11.35.

Diethyl 5-(2-phenylethyl)-1,4-(1,2-dihydropyridazine)dicarboxylate (5b). Separation by mplc of a reaction mixture obtained from 4-(2-phenylethyl)pyridazine (dichloromethane/ethyl acetate 5/1), analytic sample after mplc (dichloromethane/ethyl acetate 8/1), colourless crystals, mp=83-85°C; ms: M^+ at m/e 330, major peaks at 257 (100%), 91; ir: 2990 (ν_{N-H}), 1740, 1730, 1690 ($\nu_{C=O}$); nmr: 7.88 (d, J=4, 1H, exchangeable with D_2O), 7.52 (d, J=4, 1H, H-3, s after D_2O exchange), 7.40-7.16 (m, 5H, phenyl), 6.51 (s, 1H, H-6), 4.38-4.01 (m, 4H, 2x $\underline{CH_2}$-CH_3), 2.68-1.70 (m, 4H, CH_2-CH_2), 1.40-1.13 (m, 6H, 2x CH_2-$\underline{CH_3}$). Anal. calcd. for $C_{18}H_{22}N_2O_4$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.01; H, 6.76; N, 8.16.

Triethyl 5-methyl-1,4,6-(1,2-dihydropyridazine)tricarboxylate (6). Separation by mplc of a reaction mixture obtained from 4-methylpyridazine (dichloromethane/ethyl acetate 10/1), analytic sample after kugelrohr distillation (190°C, 10^{-1}mbar), yellow crystals, mp<25°C; ms: M^+ at m/e 312, major peaks at 279, 239 (100%), 167; ir: 3080 (ν_{N-H}), 1738, 1707, 1640 ($\nu_{C=O}$; nmr: 8.80 (d, J=4, 1H, H-2, exchangeable with D_2O), 7.45 (d, J=4Hz, 1H, H-3, s after D_2O exchange), 4.45-4.02 (m, 6H, 3x CH_2), 1.50 (s, 3H, C-5-CH_3), 1.44-1.12 (m, 9H, 3x CH_2-$\underline{CH_3}$); Anal. calcd. for $C_{14}H_{20}N_2O_6$: C, 53.84; H, 6.45; N, 8.97. Found: C, 54.04; H, 6.26; N, 8.41.

Diethyl 5-methyl-3,4-pyridazinedicarboxylate (7d). Separation by mplc of a reaction mixture obtained from 7h (method A) (dichloromethane/ethyl acetate 3/1), analytic sample after mplc (ethyl acetate), yield: 24%, yellow oil; ms: M^+ at m/z 238, major peaks at 165, 122, 94 (100%); ir: (CH_2Cl_2) 1730 ($\nu_{C=O}$); nmr: 9.30 (s, 1H, H-6), 4.70-4.33 (m, 4H, 2x CH_2), 2.47 (s, 3H, C-5-CH_3), 1.59-1.25 (m, 6H, 2x CH_2-CH_3). Hrms calcd. for $C_{11}H_{14}N_2O_4$: 238.095(4). Found: 238.095(6) ± 0.002.

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