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Hydroformylation and hydrocarbethoxylation of 1,2-dicarbethoxy-1,2,3,6-tetrahydropyridazine and 1,2-dicarbethoxy-1,2,3,4-tetrahydropyridazine

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Abstract

The unsaturated compounds 1,2-dicarbethoxy-1,2,3,6-tetrahydropyridazine **1** and 1,2-dicarbethoxy-1,2,3,4-tetrahydropyridazine **2** have been hydroformylated and hydrocarbethoxylated in the presence of some well known cobalt, rhodium, palladium and platinum catalysts. The hydroformylation reaction can be tuned by a suitable choice of the catalyst precursor and reaction conditions, thus allowing the synthesis with high selectivity of one of the two possible isomeric aldehydes. The carbonylation reaction is less synthetically useful, since it shows low activity and unsatisfactory chemo- and regio-selectivity. However, the ester 1,2,4-tricarbethoxyhexahydropyridazine **10** can be prepared in good yield from olefin **1** by using the complex $[PdCl_2(PPh_3)_2]$ as the catalyst precursor.

1. Introduction

Much attention is currently devoted to hydroformylation and related reactions of functionalized olefins for the preparation of valuable organic intermediates [1,2].

In the present paper we report the results obtained in the hydroformylation and hydrocarbethoxylation of the title compounds carried out in the presence of various catalyst precursors in order to produce with the highest yield, each of the possible aldehyde or ester reaction products.

Although compound **1** is easily obtained by the cycloaddition of butadiene to diethyl azodicarboxylate [3], we synthesised **2** *via* the selective isomerization of the pyridazine **1** catalyzed by $[RuCl_2(PPh_3)_4]$ [4].

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2. Results

The metal complexes employed as catalytic precursors are chosen from the derivatives of cobalt, rhodium, ruthenium, or platinum commonly used in hydroformylations and likely to be applied in the semi-industrial scale processes [5,6].

The results obtained in the hydroformylation of the substrates **1** and **2** are collected in Tables 1 and 2 respectively; the products formed in the reaction are depicted in Scheme 1.

The reaction produces the desired aldehydes **3** and **4**. However, there is simultaneous formation of by-products such as those deriving from hydrogenation of the substrate and the aldehydes (compounds **5**, **6** and **7**, respectively) or such as the formates (**8** and **9**).

In the hydroformylation of substrate **1** (Table 1) the rhodium-based catalysts give the highest selectivity towards aldehyde formation even at high conversion. In

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TABLE 1. Hydroformylation of 1,2-dicarbethoxy-1,2,3,6-tetrahydropyridazine in the presence of various catalyst precursors: substrate 8.7 mmol; benzene 20 ml; $P(CO) = P(H_2)$ 50 atm at 20°C

Catalyst precursor	Mmoles × 10^{-3}	T (C°)	Time (h)	Conv. (%)	Product composition (%)				Aldehyde composition (%)	
					5	3 + 4	6 + 7	8 + 9	3	4
$[Co_2(CO)_8]$	585	100	6	60.2	8.6	79.1	5.3	7.0	52.5	47.5
$[RhHCO(PPh_3)_3]$	100	80	27	60.8	10.7	85.7	0.3	3.3	99.0	1.0
$[\{Rh(COD)Cl\}_2]$/Bipy [a]	9/18	80	20	94.7	–	100	–	–	100	–
$[\{Rh(COD)Cl\}_2]$/Bipy [a]	9/18	120	5	94.6	–	99.4	0.6	–	93.9	6.1
$[Ru_3(CO)_{12}]$	310	150	24	100	77.0	10.2	–	12.8	100	–
$[PtCl_2(PPh_3)_2]/SnCl_2$	100/500	80	8	1.0	–	100	–	–	100	–
$[PtCl_2(PPh_3)_2]/SnCl_2$	100/500	100	45	19.1	–	93.2	–	6.8	100	–

[a] COD: 1,5-cyclooctadiene; Bipy: 2,2′-bipyridine.

particular, at 80°C the system $[\{Rh(COD)Cl\}_2]$/Bipy [7,8] gives aldehyde **3** with complete chemo- and regioselectivity. The activity of this system can be improved by raising the reaction temperature to 120°C without loss of chemoselectivity, but at the expense of the regioselectivity.

The cobalt catalyst displays unsatisfactory chemo- and regioselectivity, whereas the $[PtCl_2(PPh_3)_2]/SnCl_2$ system is hardly active even if highly regioselective. Among all the catalyst precursors tested, triruthenium dodecacarbonyl exhibits the highest hydrogenating activity, producing large amounts of the saturated compound **5**.

Generally the olefin **2** is less reactive towards hydroformylation than its isomer **1** (Table 2). Only the cobalt catalyst displays a satisfactory activity (100% conversion in 6 h) producing the aldehyde **4** with acceptable chemo- and regioselectivity.

Rhodium complexes display lower activities and regioselectivities, even if they give complete chemoselectivities. An increase of the reaction temperature to 120°C maintains total chemoselectivity, but the regioselectivity falls (aldehyde **3**: aldehyde **4** = 1 : 1). Also with this substrate, the ruthenium catalyst gives almost quantitatively the hydrogenation product **5**, while the platinum system is practically inactive under the conditions tested.

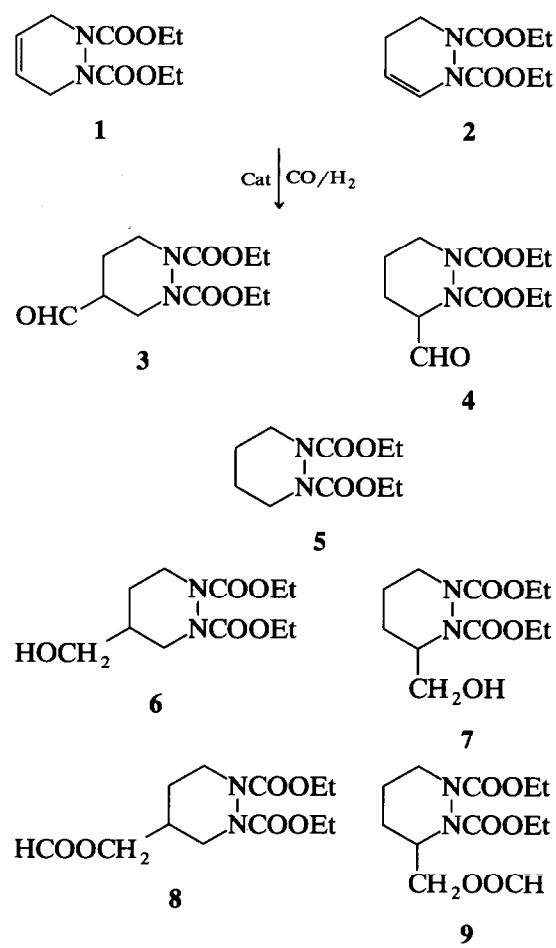
It is worthy of note that in all the hydroformylation experiments reported in Tables 1 and 2 the unreacted substrate was recovered unchanged at the end of the reaction.

The results obtained in the hydrocarbethoxylation of substrates **1** and **2** are collected in Tables 3 and 4 respectively. The products formed are depicted in Scheme 2.

The data indicate that the hydrocarbethoxylation of this type of substrate is unsatisfactory. In most cases not only is the catalytic activity of the complexes very low, but the chemoselectivity is too low for practical purposes. In fact, besides the expected esters **10** and **11**, substantial amounts of the ether **12** and dimer **13** are formed.

Only the palladium-based catalyst is able to convert the olefin **1** into the desired ester **10** with acceptable chemoselectivity and high regioselectivity (Table 3).

Among the catalytic systems used, $[Co_2(CO)_8]$ affords ether **12** as the main product, whereas $[Ru_3(CO)_{12}]$ and the rhodium complex promote the exten-



Scheme 1.

TABLE 2. Hydroformylation of 1,2-dicarbethoxy-1,2,3,4-tetrahydropyridazine in the presence of various catalyst precursors: substrate 8.7 mmol; benzene 20 ml; $P(CO) = P(H_2)$ 50 atm at 20°C

Catalyst precursor	Mmoles × 10^{-3}	T (°C)	Time (h)	Conv. (%)	Product composition (%)				Aldehyde composition (%)	
					5	3 + 4	6 + 7	8 + 9	3	4
$[Co_2(CO)_8]$	585	100	6	100	13.2	75.3	7.7	3.8	14.3	85.7
$[RhHCO(PPh_3)_3]$	100	80	70	11.2	–	100	–	–	34.0	66.0
$[\{Rh(COD)Cl\}_2]$/Bipy [a]	9/18	80	20	41.8	–	100	–	–	23.0	77.0
$[\{Rh(COD)Cl\}_2]$/Bipy [a]	9/18	120	5	68.4	–	100	–	–	49.8	50.2
$[Ru_3(CO)_{12}]$	310	150	24	100	96.6	3.4	–	–	47.1	52.9
$[PtCl_2(PPh_3)_2]$/XnCl	100/500	100	45	1.0	–	100	–	–	–	100

[a] COD: 1,5-cyclooctadiene; Bipy: 2,2'-bipyridine.

sive isomerization of the substrate to the olefin **2**, which does not react further. Moreover, both platinum catalytic precursors show a quite unsatisfactory activity.

Surprisingly, the substrate **2** (under hydroesterification conditions) is converted, in the presence of all the catalytic precursors into the ethyl ether **12** as the main product (Table 4). The catalytic systems that show hydroesterificating ability, even if in very small extent, are $[Co_2(CO)_8]$, $[\{Rh(COD)Cl\}_2]$/Bipy and $[PdCl_2(PPh_3)_2]$ (6%, 11% and 6% total esters yield respectively). Only with the cobalt catalyst is there a fairly good regioselectivity towards the formation of ester **10**. $[PdCl_2(PPh_3)_2]$ displays a slight preference for hydroesterification in the α-position with respect to the nitrogen atom, while with the rhodium complex regioselectivity is negligible.

Finally, it should be mentioned that the palladium-based catalytic system disclosed by Alper *et al.* [9],

TABLE 3. Hydrocarbethoxylation of 1,2-dicarbethoxy-1,2,3,6-tetrahydropyridazine in the presence of various catalyst precursors: substrate 8.7 mmol; substrate/catalyst precursor 50/1; benzene 20 ml; ethyl alcohol 2 ml; P(CO) 100 atm at 20°C; reaction time 89 h

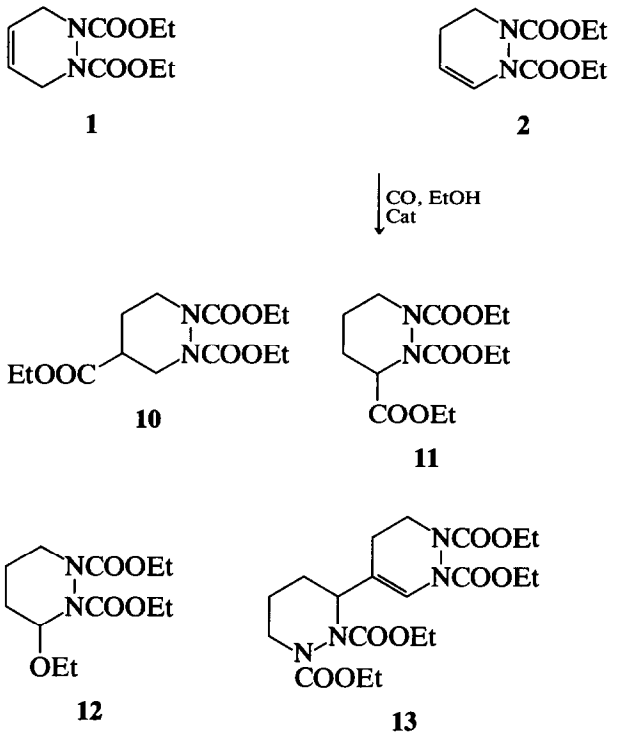
Catalyst precursor	T (°C)	Conv. (%)	Product composition (%)				Ester composition (%)	
			2	12	10 + 11	13	10	11
$[PdCl_2(PPh_3)_2]$	100	88.1	6.4	8.4	82.4	2.8	98.8	1.2
$[PtCl_2(PPh_3)_2]/SnCl_2$	100	3.6	–	–	3.6	–	100	–
$[HPtCl(PPh_3)_2]/SnCl_2$	100	61.0	61.0	91.8	3.9	0.8	100	–
$[Co_2(CO)_8]$ [a]	150	99.3	19.5	68.6	11.9	–	100	–
$[Ru_3(CO)_{12}]$ [a]	150	18.7	95.7	–	4.3	–	100	–
$[\{Rh(COD)Cl\}_2]$/Bipy [b]	150	82.7	84.4	2.1	13.5	–	100	–

[a] P(CO) = 160 atm at 20°C; [b] COD: 1,5-cyclooctadiene; Bipy: 2,2'-bipyridine.

TABLE 4. Hydrocarbethoxylation of 1,2-dicarbethoxy-1,2,3,4-tetrahydropyridazine in the presence of various catalyst precursors: substrate 8.7 mmol; substrate/catalyst precursor 50/1; benzene 20 ml; ethyl alcohol 2 ml; P(CO) 100 atm at 20°C; reaction time 89 h

Catalyst precursor	T (°C)	Conv. (%)	Product composition (%)			Ester composition (%)	
			12	10 + 11	13	10	11
$[PdCl_2(PPh_3)_2]$ [a]	100	89.2	96.7	3.3	–	27.3	72.7
$[PdCl_2(PPh_3)_2]$	100	83.2	92.7	5.7	1.6	38.6	61.4
$[HPtCl(PPh_3)_2]/SnCl_2$ [b]	100	87.7	98.4	0.7	0.9	14.3	85.7
$[HPtCl(PPh_3)_2]/SnCl_2$	100	64.5	95.5	1.1	3.4	18.2	81.8
$[Co_2(CO)_8]$ [c]	150	88.5	87.6	12.4	–	88.7	11.3
$[Ru_3(CO)_{12}]$ [c]	150	8.1	98.8	1.2	–	100	–
$[\{Rh(COD)Cl\}_2]$/Bipy [d]	150	47.8	87.3	12.7	–	45.7	54.3

[a] Substrate/catalyst precursor = 200/1, reaction time 215 h; [b] substrate/catalyst precursor = 200/1, reaction time 184 h; [c] P(CO) = 160 atm at 20°C; [d] COD: 1,5-cyclooctadiene.



Scheme 2.

which proved to be extremely efficient in the carbonylation of various olefinic substrates, is not able to produce any carbonylated product from olefin **1** or olefin **2**.

3. Discussion

The results obtained in the hydroformylation experiments carried out on pyridazine derivatives **1** and **2** present some peculiar features and deserve some comments.

As far as the catalytic activity is concerned, in the hydroformylation of both substrates, the cobalt and rhodium complexes are much more active than the platinum system. This fact can be rationalised in the following way; the substrate containing the strong donor amido-group $NCOOC_2H_5$ can compete with $SnCl_2$ for coordination to the metal [10] thus lowering the overall activity [11]. In the presence of rhodium and platinum catalysts effectively only the aldehyde **3** is produced from the olefin **1**, showing that no substrate isomerization takes place. On the contrary, using the cobalt catalyst both aldehydes **3** and **4** have been obtained, even if the isomerized olefin **2** is never detected in the reaction mixture. However, it is well known that cobalt carbonyl complexes under high CO pressure usually isomerize without release of the olefin [12].

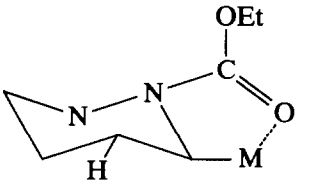


Fig. 1.

The olefin **2** is also less reactive towards hydroformylation in the presence of rhodium catalysts: this can result from steric and/or electronic factors that inhibit the coordination of the carbon–carbon double bond to the metal [13].

This behaviour is in contrast with that displayed by related cyclic enamides such as *N*-acyl-2-pyrrolines that are very reactive substrates for rhodium-catalyzed hydroformylation [14]. This difference can be ascribed to minor ring-strain in our six-membered enamide **2**, and to the fact that the EtOOCN-NCOOEt moiety is a strong electron-withdrawing system, lowering the electron density of the olefinic linkage.

The regiochemistry favouring the aldehyde **4** probably results from a directive effect of the nearest NCOOEt group on the rhodium catalyst, involving a cyclic five-membered σ-alkyl intermediate (Fig. 1), as has been suggested for a closely related system [15].

Moreover, the corresponding σ-acyl intermediate could be stabilized by the formation of a six-membered cycle (Fig. 2).

In the presence of the classical palladium carbonylation catalyst, only the pyridazine derivative **1** exhibits an acceptable reactivity in the hydrocarbethoxylation reaction (Tables 3 and 4).

The unsatisfactory chemoselectivity results from the formation of the isomerized unreactive olefin **2**, of ethyl ether **12**, and of a high boiling compound (**13**) that was identified as a dimerization product of the substrate. In particular, using $[Co_2(CO)_8]$, the ether **12** that is formed by the regioselective acid-catalysed addi-

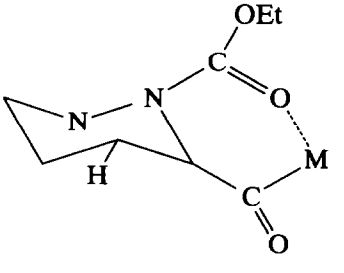


Fig. 2.

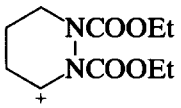


Fig. 3.

tion of ethanol to the olefinic double bond adjacent to the nitrogen atom [14], is the predominant reaction product (Table 3), probably owing to the acidic character displayed in benzene solution by hydridocarbonylcobalt complexes [16].

Only the ethyl ether derived from ethanol attack on the carbon atom on the α-position with respect to the heteroatom is formed. As acid catalysis occurs, the higher stability of the carbocation depicted in Fig. 3 accounts for the exclusive formation of ether **12** from both olefins **1** and **2**.

In our opinion, the rather basic character of both pyridazine derivatives **1** and **2** is responsible for the disappointing results obtained in the hydroesterification experiments. It is well known that this catalytic process is promoted by strong acids such as HCl [17].

Work is in progress to obtain compounds **3**, **4**, **10**, and **11** with high enantiomeric excesses by enantioselective hydroformylation or hydroesterification.

4. Experimental details

GLC analyses were performed on a Perkin-Elmer Sigma 1 system; IR spectra were recorded using a Perkin-Elmer 580B data system; GLC-mass spectra were recorded on a Shimadzu GCMS-QP 2000 system; NMR spectra were obtained on a Varian VXR 300 spectrometer operating at 299.9 MHz and 75.4 MHz for ^1H and ^{13}C NMR respectively.

4.1. Materials

1,2-Dicarbethoxy-1,2,3,6-tetrahydropyridazine **1** [3] and 1,2-dicarbethoxy-1,2,3,4-tetrahydropyridazine **2** [4] were prepared following reported procedures. Solvents were purified by standard methods [18].

The catalyst precursors $[RuCl_2(PPh_3)_4]$ [19], $[Ru_3(CO)_{12}]$ [20], $[Co_2(CO)_8]$ [16], $[\{Rh(COD)Cl\}_2]$ [21], $[HRhCO(PPh_3)_3]$ [22], $[PtCl_2(PPh_3)_2]$ [23], $[HPtCl(PPh_3)_2]$ [24], and $[PdCl_2(PPh_3)_2]$ [25] were prepared as reported.

4.2. Carbonylation procedure

Hydroformylations and hydrocarbethoxylations were carried out as described elsewhere [26]. Amounts of reactants and reaction conditions are indicated in Tables 1–4.

The conversions and the compositions of the crude products were determined by GLC using a 2 m stainless-steel column packed with Carbowax 20M (8%)/KOH (2%) on Chromosorb W (90%), or a 2 m stainless-steel column packed with OV 17 Silicone (15%) on Chromosorb GAW-DMCS (85%).

4.3. Separation and identification of products

From the crude product of the hydroformylation of olefin **2** carried out in the presence of $[Co_2(CO)_8]$ the pure aldehydes **3** and **4** were recovered after removal of the solvent by flash chromatography [silica gel 60 (70–230 mesh); 10/90 diethyl ether/hexane] as colourless oils and identified by their ^1H and ^{13}C NMR and GLC-mass spectra. The room temperature ^1H NMR spectrum of aldehyde **3** displays two signals (in an approximate two to one ratio, see below) assigned to the aldehydic proton. This is a result of a slow (on the NMR time scale) ring-inversion process, as confirmed by the broad profile of the ring carbon atom resonances in the ^{13}C NMR spectrum.

Lower amounts of 1,2-dicarbethoxyhexahydropyridazine **5**, alcohols **6** and **7**, and formates **8** and **9** were detected by GLC and identified through their GLC-mass spectra.

4.4. 1,2-Dicarbethoxy-4-formylhexahydropyridazine 3

^1H NMR (ppm, at room temperature in $CDCl_3$ solution) (the spectrum is complicated by slow ring inversion): 1.26 (t, 6H, CH_3CH_2); 1.70 (m, 1H, NCH_2CH_2); 1.90–2.20 (m, 1H, NCH_2CH_2); 2.67 (broad m, 1H, CH–CHO); 2.7–3.5 (broad signal, 2H, two NCH–H); 3.9–4.6 (broad signal partially overlapped by the CH_2CH_3 quartet, 2H, two NCH–H); 4.19 (q, 4H, CH_2CH_3); 9.65 (s, 0.68H, CHO); 9.83 (d, 0.32H, CHO) (slow exchanging ax. and eq. CHO).

$^{13}C\{^1H\}$ NMR (ppm, at room temperature in C_6D_6 solution) (some carbon atoms give rise to two broad separate resonances owing to slow ring inversion: 14.49 (2C, CH_3); 21.90 and 23.80 (1C, NCH_2CH_2); 44.03 (2C, NCH_2); 45.08 and 46.42 (1C, CH-CHO); 62.33 (2C, CH_2CH_3); 155.16 (2C, COO); 200.10 and 201.16 (1C, CHO).

GLC-mass spectrum showed peaks at *m/e*: 258 $(M)^+$, 213 $(M - OC_2H_5)^+$, 186 $(M - CO_2 - C_2H_4)^+$, 185 $(M - COOC_2H_5)^+$, 158 $(186 - C_2H_4$ or $C_6H_{10}N_2O_3)^+$, 157 $(186 - CHO$ or $186 - C_2H_5)^+$, 142 $(CH_2C(CHO)=NCOOC_2H_5)^+$, 141 $(142 - H)^+$, 139 $(C_6H_7N_2O_2)^+$, 117 $(C_5H_{11}NO_2)^+$, 113 $(C_5H_7NO_2)^+$.

4.5. 1,2-Dicarbethoxy-3-formylhexahydropyridazine 4

^1H NMR (ppm, at room temperature in $CDCl_3$ solution): 1.20 (t, 3H, CH_3); 1.24 (t, 3H, CH_3); 1.45–1.70 (m, 1H, $NCH_2CH_2CH_2$ and 2H, NCH_2CH_2); 2.05–2.23 (m, 1H, $NCH_2CH_2CH_2$); 2.86 (m, 1H, NCH_2); 4.00 (m, 1H, NCH_2); 4.20 (m, 4H, $COOCH_2$);

4.75 (broad s, 1H, C*H*CHO); 9.73–9.79 (broad s, 1H, CHO) (slow exchanging ax. and eq. C*H*O).

^{13}C-{^1H} NMR (ppm, at room temperature in $CDCl_3$ solution) (some carbon atoms give rise to two broad separate resonances owing to slow ring inversion): 14.47 (2C, CH_3); 20.13 and 20.43 (1C, NCH_2CH_2); 21.46 and 22.18 (1C, $NCH_2CH_2CH_2$); 43.54 and 45.30 (1C, NCH_2); 62.15 and 62.39 (1C, CH-CHO); 63.14 (2C, CH_2CH_3); 154.90 (1C, COO); 155.90 (1C, COO); 200.55 and 201.09 (1C, CHO).

GLC-mass spectrum showed peaks at *m/e*: 258 $(M)^+$, 229 $(M - CHO)^+$, 185 $(M - COOC_2H_5)^+$, 157 $(229 - CO_2 - C_2H_4)^+$, 142 $(CH_2C(CHO)=NCOOC_2H_5)^+$, 141 $(142 - H)^+$, 129 ($C_5H_7NO_3$ or $C_6H_{11}NO_2)^+$, 111 $(C_5H_5NO_2)^+$, 97 $(C_4H_3NO_2)^+$, 68 (C_4H_6N or $C_3H_4N_2)^+$.

4.6. 1,2-Dicarbethoxyhexahydropyridazine 5

GLC-mass spectrum showed peaks at *m/e*: 230 $(M)^+$, 185 $(M - OC_2H_5)^+$, 158 $(M - CO_2 - C_2H_4)^+$, 157 $(M - COOC_2H_5)^+$, 130 $(158 - C_2H_4)^+$, 113 $(158 - OC_2H_5)^+$, 86 $(C_4H_{10}N_2)^+$, 85 $(C_4H_9N_2)^+$, 58 ($C_2H_6N_2)^+$, 56 (C_4H_8 or $C_2H_4N_2)^+$.

4.7. 1,2-Dicarbethoxy-4-hydroxymethylhexahydropyridazine 6

GLC-mass spectrum showed peaks at *m/e*: 260 $(M)^+$, 229 $(M - CH_2OH)^+$, 215 $(M - OC_2H_5)^+$, 185 $(215 - HCHO)^+$, 157 $(185 - C_2H_4$ or $185 - CO)^+$, 141 $(C_7H_{13}N_2O)^+$, 129 $(C_6H_{11}NO_2)^+$, 111 $(C_5H_7N_2O)^+$, 85 $(C_5H_{11}N)^+$, 84 $(C_4H_6NO)^+$, 68 (C_4H_6N or $C_3H_4N_2)^+$.

4.8. 1,2-Dicarbethoxy-3-hydroxymethylhexahydropyridazine 7

GLC-mass spectrum showed peaks at *m/e*: 229 $(M - CH_2OH)^+$, 215 $(M - OC_2H_5)^+$, 188 $(M - CO_2 - C_2H_4)^+$, 187 $(M - COOC_2H_5)^+$, 185 $(215 - HCHO)^+$, 157 $(185 - C_2H_4$ or $185 - CO)^+$, 156 $(157 - H)^+$, 145 $(C_6H_{11}NO_3)^+$, 143 $(188 - OC_2H_5)^+$, 141 $(C_7H_{13}N_2O)^+$, 130 ($C_6H_{12}NO_2$ or $C_5H_8NO_3)^+$, 129 $(C_6H_{11}NO_2)^+$, 117 ($145 - C_2H_4$ or $C_4H_7NO_3)^+$, 111 $(143 - CH_3OH)^+$, 89 $(C_3H_9N_2O)^+$, 84 $(C_4H_6NO)^+$, 83 $(C_4H_7N_2)^+$, 71 $(C_3H_7N_2)^+$, 58 $(C_3H_6O)^+$.

4.9. 1,2-Dicarbethoxy-4-hydroxymethyl-O-formylhexahydropyridazine 8

GLC-mass spectrum showed peaks at *m/e*: 288 $(M)^+$, 243 $(M - OC_2H_5)^+$, 216 $(M - CO_2 - C_2H_4)^+$, 215 $(M - 73)^+$, 171 $(243 - 72)^+$, 169 $(243 - 74)^+$, 144 $(216 - 72)^+$, 143 $(216 - 73)^+$, 125 $(169 - CO_2)^+$, 114 $(143 - 29)^+$, 97 $(125 - CO)^+$, 68 (C_4H_6N or $C_3H_4N_2)^+$.

4.10. 1,2-Dicarbethoxy-3-hydroxymethyl-O-formylhexahydropyridazine 9

GLC-mass spectrum showed peaks at *m/e*: 288 $(M)^+$, 243 $(M - OC_2H_5)^+$, 229 $(M - HCOOCH_2)^+$, 216 $(M - CO_2 - C_2H_4)^+$, 185 $(243 - 58)^+$, 169 $(243 - 74)^+$, 157 $(229 - 72$ or $216 - 59)^+$, 129 $(C_5H_9N_2O_2)^+$, 125 $(169 - CO_2)^+$, 111 $(157 - C_2H_5OH)^+$, 97 $(125 - CO)^+$, 83 $(97 - CH_2)^+$, 68 (C_4H_6N or $C_3H_4N_2)^+$.

From the crude product of the hydrocarbethoxylations the pure ether **12** and the dimer **13** were recovered after removal of the solvent by flash chromatography (silica gel, diethyl ether–hexane from 10/90 up to 50/50) as colourless oils and identified by their ^1H NMR and GLC-mass spectra. The ester **10** and **11** were identified by their GLC-mass spectra.

4.11. 1,2,4-Tricarbethoxyhexahydropyridazine 10

GLC-mass spectrum showed peaks at m/e: 302 $(M)^+$, 257 $(M - OC_2H_5)^+$, 230 $(M - 72)^+$, 229 $(M - 73)^+$, 185 $(230 - OC_2H_5)^+$, 183 $(229 - C_2H_5OH)^+$, 157 $(229 - 72)^+$, 155 $(183 - C_2H_4)^+$, 129 $(157 - C_2H_4)^+$, 128 $(157 - C_2H_4 - H)^+$, 111 $(C_5H_7N_2O)^+$, 83 $(111 - CO)^+$, 68 (C_4H_6N or $C_3H_4N_2)^+$.

4.12. 1,2,3-Tricarbethoxyhexahydropyridazine 11

GLC-mass spectrum showed peaks at *m/e*: 302 $(M)^+$, 229 $(M - 73)^+$, 185 $(230 - OC_2H_5)^+$, 158 $(230 - 72)^+$, 157 $(229 - 72)^+$, 130 $(158 - C_2H_4)^+$, 129 $(157 - C_2H_4)^+$, 111 $(C_5H_7N_2O)^+$, 101 $(CH_2=NCOOC_2H_5)^+$, 83 $(111 - CO)^+$, 73 $(101 - C_2H_4$ or $COOC_2H_5)^+$, 68 (C_4H_6N or $C_3H_4N_2)^+$.

4.13. 1,2-Dicarbethoxy-3-ethoxyhexahydropyridazine 12

^1H NMR (ppm, at room temperature in $CDCl_3$ solution): 0.90–1.20 (m, 9H, CH_3); 1.26 (dt, 1H, $NCH_2CH_2CH_2$); 1.64 (m, 2H, NCH_2CH_2); 1.82 (m, 1H, $NCH_2CH_2CH_2$); 2.86 (m, 1H, NCH_2); 3.35 (m, 1H, OCH_2); 3.62 (m, 1H, OCH_2); 3.96 (m, 1H, NCH_2); 4.10 (m, 4H, $COOCH_2$); 5.25 (broad s, 1H, $HCOCH_2CH_3$).

GLC-mass spectrum showed peaks at *m/e*: 274 $(M)^+$, 229 $(M - OC_2H_5)^+$, 185 $(229 - CO_2)^+$, 157 $(229 - CO_2 - C_2H_4)^+$, 156 $(229 - COOC_2H_5)^+$, 117 ($C_4H_7NO_3)^+$, 111 $(C_5H_7N_2O)^+$, 99 $(C_4H_7N_2O)^+$, 98 ($C_4H_6N_2O)^+$, 89 $(C_2H_3NO_3)^+$, 85 $(C_4H_9N_2)^+$.

4.14. Dimeric compound 13

^1H NMR (ppm, at room temperature in $CDCl_3$ solution): 1.00–1.30 (m, 12H, CH_2CH_3); 1.50 (m, 1H); 1.70–2.09 (broad m, 3H); 2.18 (broad m, 1H); 2.98 (broad m, 2H); 3.90–4.40 (broad m, 8H, $COOCH_2CH_3$ and 3H); 4.79 (broad m, 1H); 6.90 (broad m, 1H).

^{13}C-{^1H} NMR (ppm, at room temperature in $CDCl_3$ solution, some signals are broad owing to slow ring

inversion): 13.88 (4C, CH_3); 19.08 (1C, NCH=CCH_2); 23.04 (broad, 2C, $NCHCH_2CH_2CH_2N$); 42.3–43.2 (broad, 2C, two NCH_2); 55.07–55.76 (broad, 1C, $NNCH(C{=}CHNH)CH_2CH_2CH_2$); 61.36 91C, one $NCOOCH_2$); 61.98 (3C, three $NCOOCH_2$), 115.31 (1C, NCH=$C(CHNNCH_2CH_2CH_2)CH_2$); 121.35 (1C, NCH=C); 151.66 (1C, $NCOOCH_2CH_3$); 154.60 (1C, $NCOOCH_2CH_3$); 155.57 (2C, two $NCOOCH_2CH_3$).

GLC-mass spectrum showed peaks at *m/e*: 456 $(M)^+$, 411 $(M - OC_2H_5)^+$, 384 $(M - CO_2 - C_2H_4)^+$, 383 $(M - COOC_2H_5)^+$, 367 $(M - 89)^+$, 339 (M − 117 or 384 − $OC_2H_5)^+$, 311 $(M - CO_2 - C_2H_4 - COOC_2H_5)^+$, 295 $(367 - CO_2 - C_2H_4)^+$, 294 $(339 - OC_2H_5)^+$, 282 $(M - C_2H_5OOCN{=}NCOOC_2H_5)^+$, 280 $(M - C_2H_5OOCNHNHCOOC_2H_5)^+$, 267 (M − 72 − 72 − 45)$^+$, 265 (M − 73 − 73 − 45)$^+$, 236 $(267 - CH_2CH_3)^+$, 223 $(295 - CO_2 - C_2H_4)^+$, 208 $(280 - CO_2 - C_2H_4)^+$, 207 $(280 - COOC_2H_5)^+$, 195 (282 − 87)$^+$, 191 $(236 - OC_2H_5)^+$, 157 $(229 - CO_2 - C_2H_4)^+$, 149 $(195 - C_2H_5OH)^+$, 135 $(208 - COOC_2H_5)^+$, 117 $(C_5H_{11}NO_2)^+$, 111 $(C_5H_5NO_2)^+$.

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