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CYCLIZATIONS OF 1-METHYL-1-(3-PYRIDAZINYL)HYDRAZONES[1]

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Abstract — Under varying conditions 1-methyl-1-(3-pyridazinyl)hydrazones — depending on the character of the heteroaromatic substituents — undergo cyclization to molecules of different structures. The structures of the new compounds were proved by ir-, ^{1}H- and ^{13}C-nmr as well mass spectroscopy.

INTRODUCTION

Several pyridazinylhydrazine derivatives are currently being used as hypotensive agents.[2,3] A representative of this group[4] prepared by us is now under clinical trial. These results have encouraged us to make a few synthetic efforts in this field to synthesize new condensed systems starting from these hydrazones.

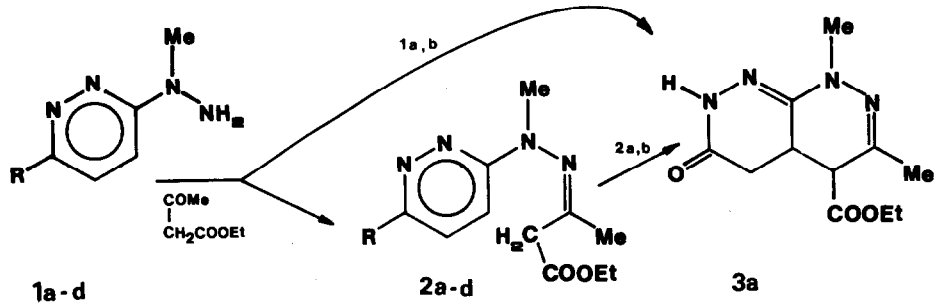
Previously we reported the cyclization of pyridazinylhydrazones under thermal or basic conditions to give pyridazinylpyrazolines[5] and not condensed system. However, bicyclic N-condensed [6+6]-ring systems can often be obtained in this way from different heterocycles.[6] In order to avoid the formation of pyrazoles we carried out the reactions with 1-methyl-substituted pyridazinylhydrazones.

Reactions of N,N-disubstituted hydrazones have not extensively been studied. It was only reported that hydrazones formed from 6-(1-alkylhydrazino)isocytosines readily afforded pyrimidopyridazines and pyrimidodiazepines readily afforded pyrimidopyridazines and pyrimidodiazepines, respectively.[7,8]

RESULTS AND DISCUSSION

When the convenient precursors **2**[4] (prepared by the reaction of 1-methyl-1-(3-pyridazinyl)hydrazines **1** with β-ketoesters), were allowed to react under varying conditions (thermal or basic) products of different structure have been obtained depending on the character of the substituent in Pos. 6 of the pyridazine ring.

Thermal reactions were carried out by heating the components (a) or the hydrazones (b) in Dowtherm at 240-250 °C for a few minutes. Both the above reaction paths from either **1a,b** or **2a,b** gave exclusively a pyridazino[3,4-c] pyridazine derivative **3a** (Scheme 1):



a (R: Cl), b (R: OMe), c (R: Mf, morpholino), d (R: Ph)

Scheme 1

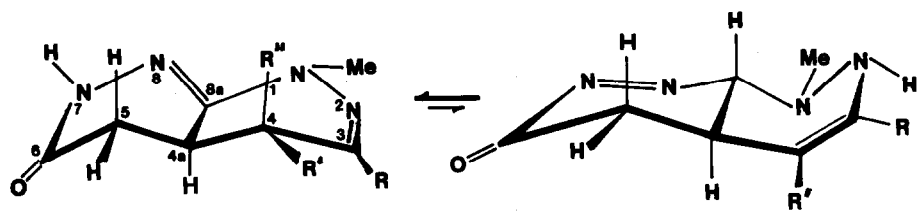
The reaction proceeds probably via a pyridazinone intermediate derived from 2a,b by hydrolysis of the unstable 6-chloro or -methoxy group by one mole of water formed by condensation (or in the presence of traces of water). This intermediate undergoes an intramolecular Michael addition (nucleophilic attack of the negatively polarized α-methylene carbon on C-4) leading to 3a.

Ir, ^{1}H- and ^{13}C-nmr data of the new compounds are given in the Experimental. Spectral parameters proving structure of 3a are as follows:

1) The diffuse νNH band (3280-2750 cm^{-1}) is characteristic of amides[9a] and the amide-I band at 1655 cm^{-1} in the ir;

2) The values of the coupling constants J(H-4,H-4a) = 12 Hz and J(H-4a,H-5) = 16 Hz determined from the ^{1}H-nmr multiplets (t+dd+dt+d) of an ABMX spin-system consists of the H-4,4a,5,5' atoms, proving the diaxial positions of these proton-pairs (Fig. 1). From these couplings (i) the trans-arrangement of H-4 and H-4a and (ii) the conformation shown in Fig. 1 having all substituents (C-Me, N-Me and the COOEt groups) in equatorial position are concluded;

3) Apart form the ^{13}C-nmr signals of the substituents (three methyl and one O-methylene lines), there are found four characteristic downfield shifted lines (corresponding to two carbonyl and two imine carbons) and three lines



3a (R: Me, R': COOEt, R":H)
7a (R: COOEt, R': H, R":Ac)

3b (R: Me, R': COOEt)
7b (R: COOEt, R': Ac)

Fig. 1

in the region of sp^3 carbons corresponding to the skeletal atoms C-4,4a,5 (cf. Experimental).

The tautomeric structure 3b with trans-annelated rings can be excluded on the basis of the following facts:

1) No strongly deshielded carbon is present among the sp^3 carbons, a phenomenon characteristic of a methine group bearing two nitrogens (N-CH-N);

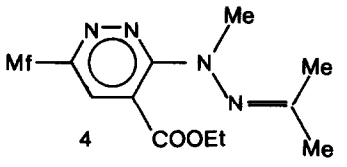
2) Due to polarization of the enamino-carbonyl system in structure 3b the shift difference between signals of the two sp^2 carbons would be much larger than the observed one;[10a]

3) Allylic coupling between the C-methyl hydrogens and the H-4 atom was observed (0.6 Hz): a similar small split due to coupling of the methyl- and NH-hydrogens is very improbable;

4) In the proton coupled ^{13}C-nmr spectrum the C-8a signal is a complex multiplet due to ^3J(C,H) couplings with the N-methyl and 5-methylene hydrogens and the H-4 atom, as well as to ^2J(C,H) interaction with H-4a, whereas in the case of 3b the corresponding C-3 signal would be a doublet or a double doublet.

Considering the steric hindrances which are significantly higher in all other possible structures with different configurations and conformations, the formation of the most stable, sterically most favourable one is plausible on the basis of the reaction conditions (thermodynamic control).

The behaviour towards heating of hydrazones having non-hydrolizable electron donating substituent in the pyridazine ring is dramatically different from that shown by compounds so far considered. Heating of 2c or 1c with ethyl acetoacetate in Dowtherm leads to the formation of the 4-ethoxycarbonyl-hydrazone derivative 4.

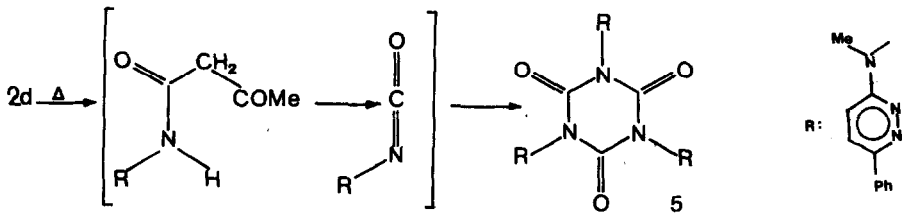


The following spectral data proved the structure of compound 4:

1) The low frequency (1720 cm^{-1}) of the ester νC=O band in the ir is characteristic of conjugated groups (cf. the higher frequency of 3a);

2) In ^{1}H-nmr spectrum appears only one singlet arising from heteroaromatic hydrogens. There are two methyl singlets in the shift region of groups attached to sp^2 carbons. There are no signals assignable to a methylene group or to NH and =CH hydrogens (due to the tautomerisation $-N=C-CH_2- \rightleftharpoons -NH-C=CH-$);

3) Apart from the lines of the substituents (morpholino, COOEt, N-methyl and two C-methyl groups) there are five lines in the ^{13}C-nmr spectrum having chemical shifts characteristic of sp^2 carbons. The high intensity of one of these lines made the assignment to the H-substituted C-5 atom straightforward. The only upfield line of substituted sp^2 carbons is originating from C-4 (without nitrogen neighbours).



Scheme 2

The thermal reaction of compound 2d with the electron-attracting phenyl group afforded only product 5. The reaction may be interpreted as a know rearrangement to hydrazide[11] followed by C-C bond fission to N-isocyanate intermediate, which was then stabilized as the triazinetrione 5 (Scheme 2). The postulated structure of 5 was deduced from the following spectral features:

1) In the spectra of 5 all signals corresponding to the acetoacetate moiety are absent;

2) All characteristics of the N-methyl and phenyl groups and the 3,6-disubstituted pyridazine ring are identifiable in all spectra;

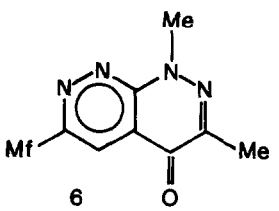
3) A very intense amide-I band appears in the ir-spectrum at 1660 cm^{-1}.

4) No further signals, except the substituents mentioned above appear in the ^{1}H-nmr spectrum.

5) In addition to the lines of the phenyl and pyridazine ring and the N-Me group, respectively, the ^{13}C-nmr spectrum shows only one signal at 155.5 ppm.

6) The mass spectrum gives an ion peak at m/z 226. However, from the ir frequencies and the carbon chemical shifts the trimeric structure follows unambiguously (the monomeric cumulene[9b] and the dimeric diazetidinedione[12] would give significantly higher ir frequencies and the former one would show a much more downfield shifted carbon signal[10b]).

Reactions under basic conditions were carried out by heating of 2a-d in an alcohol containing NaOR. The reaction led only in the case of 2c to an isolable product, i. e. to the pyridazino[3,4-c]pyridazine derivative 6.



6

The spectroscopic characteristics confirming the structure of 6 are as follows:

1) The ir bands and nmr signals of the CH_2COOEt moiety of 2c are missing in the spectra of 6.

2) A very intense amide-I band appears in the ir spectrum at 1625 cm^{-1}.

3) In addition to the C-methyl and N-methyl singlets and the two triplets of the morpholine ring only one singlet of 1H-intensity appears in the ^{1}H-nmr spectrum at 7.46 ppm corresponding to an isolated heteroaromatic H atom.

4) Apart from the two-two lines of the methyl and methylene carbons, the ^{13}C-nmr spectrum shows six signals. One of them can be assigned to the H-substituted C-5 atom on the basis of its outstanding intensity and upfield position; the downfield one at 172 ppm is assigned to the 4-carbonyl carbon. Of the four heteroaromatic carbons C-4a is more shielded having C atoms only as neighbours and C-8a is strongly deshielded by the two attached N atoms.
5) High-resolution mass spectrum shows a molecular ion of 261.

At present, we cannot give a satisfactory explanation for this unusual reaction occurring with the loss of one C atom. Again we proved that the C=O and not the CH_2 carbon was eliminated: 2c has been labelled by ^{14}C using ^{14}C-labelled ethyl (1,3-^{14}C)-3-oxobutanoate prepared from ethyl 1-^{14}C-acetate. Since the labelled oxo-carbon atom is involved in the reaction, an intermolecular isotope effect must be taken into consideration in the formation of 1,3-^{14}C-2c. This means that the experiment can be regarded as a proof of the elimination of an ethoxycarbonyl group, if the specific activity of the product (3-^{14}C-6) is equal to, or lower than the half of that of the labelled starting hydrazone. This latter was the case: the specific activity of 1,3-^{14}C-2c (10.98 MBq/mmol) was reduced to 4.84 MBq/mmol in 3-^{14}C-6.

We tried to prepare 6 by an independent synthesis, but ethyl pyruvate N-(6-morpholino-3-pyridazinyl)-N-methylhydrazone failed to react to 6 under the same conditions. The possible formation of the hydrazone as last intermediate and its subsequent cyclization can be ruled out by this fact.

Reaction of α- or γ-ketoesters with pyridazinylhydrazines 2a-d did not afford any isolable product. Extension of this reaction of 2a with α,γ-diketoesters might lead to 6-, 7- and 8-membered condensed systems, due to the different reaction centres. Reaction of 1a with ethyl 2,4-dioxovalerate in methanol at room temperature gave only one product, a pyridazino[3,4-c]pyridazine derivative 7 (Fig. 1). The probable mechanism is analogous to the formation of 3a: the first step is a hydrazone formation at the more reactive α-keto function followed by hydrolysis of the C-Cl bond. The Michael addition of this intermediate yields 7.

The ir, ^{1}H- and ^{13}C-nmr spectra of 7 are very similar to those of 3a. The most remarkable difference is in the value (6.3 Hz) of the coupling J(H-4,H-4a). It suggests a different conformation or configuration C-4.

The higher amide-I and lower νC=O (ester) ir frequencies of 7 can be attributed to the stronger conjugation among the -CO-NH-N=C-NMe-N=CMe- chain in 3a (negative polarization of the amide moiety) and the conjugation of the ester group in 7a, respectively. A dramatic deshielding of H-4 in the ^{1}H-nmr spectrum of 7a can be observed in comparison with 3a (the shift difference is 1.07 ppm). It can be explained by the different chemical environment (geminal acetyl and vicinal ester groups instead of ester and methyl ones,

respectively, in analogous positions) and by change from axial to equatorial position of H-4 (equatorial hydrogens on saturated or partly saturated six membered rings are deshielded in comparison to their axial counterparts[10c]) in accordance with the J(H-4,H-4a) value (6.3 Hz).

As the conformation of the tetrahydropyridazinone ring is determined by the high value (14.5 Hz) of the coupling J(H-4a,H-5'ax), structures 7a and 7b differing in C-4 configuration and in conformation of the ring involving this carbon atom are to be considered.

Structure 7b is, however, improbable due to strong steric interactions, e.g. between H-4a and the acetyl group or between the latter and the ethoxycarbonyl group. The 6.3 Hz value of J(H-4,H-4a) is a further counterargument: the corresponding dihedral angle is namely ∿90° in 7b and according to Karplus relation[13] a significant smaller split would be expected.

The structure similar to 3a is also evidenced by the similar ^{13}C-nmr chemical shifts of the C-4,4a,5 atoms. The C-3 signal is a doublet in the proton coupled spectrum due to ^{3}J(C,H) interaction with H-4a, while the C-8a signal is a very complex multiplet. In case of the tautomer 7b for the analogous C-4 and C-3 signals a reversed multiplicity (complex multiplet at 129.4 ppm and a doublet at 143.6 ppm would be expected).

A definite Overhauser interaction between H-5'ax and the acetyl methyl hydrogens measured by DNOE experiment[16d] was observed, proving their sterically close arrangements and thereby the structure 7a unambiguously.

EXPERIMENTAL

All melting points were taken on a Boetius apparatus and are uncorrected. TLC was performed by using Merck plates. Column chromatography was employed by using Kieselgel 60 (0.063-0.1 mesh).

Ir-spectra were run in BKr discs on a Bruker IFS-113v vacuum optic FT-spectrometer equipped with an Aspect 2000 computer.

Nmr spectra were recorded at room temperature in $CDCl_3$ or DMSO-d_6 solution in 5 or 10 mm tubes on a Bruker WM-250 FT-spectrometer controlled by an Aspect 2000 computer at 250 (H-1) and 63 (C-13) MHz, respectively, using the deuterium signal of the solvent as the lock and TMS as internal standard. Complete proton noise decoupling (∿3 W) for the C-13 spectra was used. DNOE experiments for 7a were performed with the Bruker microprogramme 12.5 in the Aspect 2000 Pulse Programmer. Gated decoupling to generate NOE was used, delay time 30 s, decoupling power 40 mW. C-13 nmr assignments were proved for 3a and 7a by DEPT measurements and proton-coupled spectra. DEPT[14] spectra were run in a standard way,[15] using only the Θ=135° pulse to separate CH/CH_3 and CH_2 lines phased "up and down", respectively.

Mass spectra were recorded on a Varian MAT SM1 double focusing spectrometer. The operating parameters were: an accelerating potential of 8 KV, 70 eV electron energy, an electron current of 300 mA, a source temperature of 250 °C and a resolution of 1 250.

Radiochemical purity was checked by TLC carried out on silicagel HF_{254} (Merck) using benzene-methanol 85:15 solvent system, and a Berthold TLC scanner Model LB 2723 for evaluation. Radioactivity was measured by the liquid scintillation technique using a Pacard TRI-CARB Model 2660 spectrometer.

The starting materials were prepared by standard methods[3] (see Table 1).

Thermal reactions. – Method A. A mixture of 1 g a hydrazone 2 and 5 ml of Dowtherm was heated in an oil bath (preheated) at 240-250 °C for 5-10 min. After cooling and trituration of the reaction mixture by petroleum ether the solid products obtained were recrystallized from ethanol to give 3, 5 and 6.

Table 1. Physical and analytical data of the compounds 1a-d and 2a-d

Compound	Yield %	M.p. °C	Formula	Mol. weight	Analysis (%), Calcd./Found C	H	N
1a	65	102.104	$C_5H_7ClN_4$	158.59	37.87/37.94	4.45/4.53	35.33/35.21
1b	72	oil	$C_6H_{10}N_4O$	154.17	46.74/46.49	6.54/6.71	36.34/36.17
1c	95	111-112[a]	$C_9H_{15}N_5O$	209.25	51.66/51.61	7.23/7.32	33.47/33.34
1d	80	133-134	$C_{11}H_{12}N_4$	201.10	65.69/65.78	6.02/6.14	27.86/27.69
2a	55	74-75	$C_{11}H_{15}ClN_4O_2$	270.72	48.80/48.75	5.59/5.68	20.70/20.56
2b	82	oil	$C_{12}H_{18}N_4O_3$	266.29	54.12/53.98	6.81/6.89	21.04/20.92
2c	71	121-122	$C_{15}H_{23}N_5O_3$	321.37	56.06/56.12	7.21/7.38	21.79/21.72
2d	42	112-114	$C_{17}H_{20}N_4O_2$	312.36	65.36/65.32	6.45/6.57	17.94/17.96
_b	53	120-121	$C_{14}H_{21}N_5O_3$	307.35	54.71/54.64	6.89/6.97	22.79/22.68

[a] HCl salt, m.p. 175-8 °C; [b] Ethyl pyruvate N-(6-morpholino-3-pyridazinyl)-N-methylhydrazone

Method B. A mixture of the equimolar amounts of a hydrazine 1a and $AcCH_2COOEt$ in Dowtherm was heated in an oil bath (preheated) at 140 °C for 20 min., then at 240-250 °C for 5 min. The workup was the same as mentioned above, e.g. 3 was prepared from 1a in this way.

Method C. See 7a.

1,3-Dimethyl-4-ethoxycarbonyl-1,4,4a,5-tetrahydropyridazino[3,4-c]pyridazin-6(7H)-one (3a)

Yield: 12 % (from 2a), 5 % (from 1a), M.p.: 182-4 °C (EtOH). $C_{11}H_{16}N_4O_3$ (252.27): cal./found C, 52.37/52.39; H, 6.39/6.44; N, 22.21/22.17. Uv (96 % EtOH): λ_{max}(e) = 234 (0.183) and 312 (0.367) nm. Ir (KBr): νNH: 3280-2750, νC=O(ester): 1740, amide-I: 1655 cm^{-1}. ^{1}H-nmr (δ, $CDCl_3$): CH_3(Et), t(3H): 1.34 (J: 7 Hz), CH_3, d(3H): 1.96 (J: 0.6 Hz), CH_2(5), t+dd(2x1H): 2.37 (J: 16 Hz) and 2.55 (J: 16 and 8 Hz), CH(4), d(1H): 3.18 (J: 12 Hz), NCH_3, s(3H): 3.28, CH(4a), dt(1H): 3.44, OCH_2, qa(2H): 4.30, NH(7), broad s(1H): 8.78 ppm. ^{13}C-nmr (δ, $CDCl_3$): CH_3(Et): 14.2, CH_3(3): 20.3, C-4a,5: 31.6, 32.1, NCH_3: 38.7, C-4: 47.9, OCH_2: 62.1, C-3: 142.1, C-8a: 147.7, C=O(ester): 165.4, C-6: 169.6 ppm. Mass: m/e 252 (100 %).

1-(4-Ethoxycarbonyl-6-morpholino-3-pyridazinyl)-1-methyl-2-isopropylidenehydrazine (4)

Yield: 30.5 %, M.p.: 121-2 °C (EtOH). $C_{15}H_{23}N_5O_3$ (321.37): cal./found C, 56.05/56.11; H, 7.21/7.27; N, 21.79/21.69. Uv (96 % EtOH): λ_{max}(e) = 306 (0.493) and 484 (0.06) nm. Ir (KBr): νC=O: 1720, νC=N: 1575, νC-O(Mf): 1120 cm^{-1}. ^{1}H-nmr (δ, $CDCl_3$): CH_3(Et), t(3H): 1.36 (J: 7 Hz), $=CCH_3$, 2xs(2x3H): 2.19 and 2.29, NCH_2, ∿t(4H): 3.36, NCH_3, s(3H): 3.54, OCH_2(Mf), ∿t(4H): 3.75, OCH_2(Et), qa(2H): 4.32, H-5, s(1H): 8.14 ppm. ^{13}C-nmr (δ, $CDCl_3$): CH_3(Et): 12.2 $=C(CH_3)_2$: 14.1, 20.4, NCH_3: 40.9, NCH_2: 46.4, OCH_2(Et): 61.4, OCH_2(Mf): 66.8, C-5: 125.9, C-4: 128.6, $=C(CH_3)_2$: 137.5, C-3: 150.6, C-6: 159.1, C=O: 165.1 ppm. Mass: m/e 321 (100 %).

1,3,5-tris[1-(6-Phenyl-3-pyridazinyl)-1-methylamino-1,3,5-triazine-2,4,6(1H,3H,5H)]-trione (5)

Yield: 13 %, M.p.: 294-6 °C (EtOH). $C_{36}H_{30}N_{12}O_3$ (678.70) calc./found C, 63.70/63.64; H, 4.46/4.52; N, 24.77/24.63. Uv (96 % EtOH): λ_{max}(e) = 237 (0.533), 281 (0.870), 380 (0.060) nm. Ir (KBr): amide-I: 1665 cm^{-1}. ^{1}H-nmr (δ, DMSO-d_6): NCH_3, s(3H): 3.90, $ArH^{m,p}$, m(3H): ∿7.6, ArH^{o}, dd(2H): 8.10, H-4, d(1H): 8.12, (J: 10 Hz), H-5, d(1H): 8.43 ppm. ^{13}C-nmr (δ, DMSO-d_6): NCH_3: 37.0, C-4: 121.4, C-5: 124.6, C-3',5'(Ph): 128.6, C-2',6'(Ph): 130.6, C-4'(Ph): 132.2, C-1'(Ph), C-6: 135.5, 136.1, C-3: 153.3, C=O: 155.5 ppm. Mass m/e 226 (100%).

1,3-Dimethyl-6-morpholinopyridazino[3,4-c]pyridazin-4(1H)-on (6)

A mixture of 5 mmol of 2c and $MeO(CH_2)_2ONa$ solution, prepared from 0.15 g (6.5 g-atom) of freshly cut Na and 24 mL of anhydr. 2-methoxyethanol, was heated at 80 °C for 9h. After cooling to 5-10 °C the mixture was adjusted to pH 6.5 with 10 % HCl diluted with water (10 mL) and then allowed to stand at RT. Yield: 24 % (with NaOMe: 13 %, with $KOBu^t$: 7 %). M.p.: 216-7 °C (EtOH) red needles. $C_{12}H_{15}N_5O_2$ (261.28): cal./found: C, 55.16/55.17; H, 5.79/5.86; N, 26.81=26.74. Uv (96 % EtOH): λ_{max}(e) = 239 (0.746), 303 (0.465), 465 (0.214) nm. Ir (KBr): amide-I: 1625, νC=N: 1585, νC-O: 1120, 1110 cm^{-1}. H-nmr (δ, $CDCl_3$): CH_3(3), s(3H): 2.38,

NCH_2, ∿t(4H): 3.72, OCH_2, ∿t(4H): 3.92, NCH_3, s(3H): 4.30, H-5, s(1H): 7.46 ppm. ^{13}C-nmr (δ, $CDCl_3$): CH_3(3): 16.5, NCH_3: 41.1, NCH_2: 46.1, OCH_2: 66.5, C-5: 103.4, C-4a: 119.2, C-3,6: 146.0, 147.7, C-8a: 159.3, C=O(4): 172.1 ppm.

4-Acetyl-3-ethoxycarbonyl-1-methyl-1,4,4a,5-tetrahydro|3,4-c|pyridazin-6(7H)-one (7a)

A mixture of 1.6 g (10 mmol) of 1a and 1.7 g (10.75 mmol) ethyl 2,4-dioxovalerate in ethanol (16 mL) was stirred at room temperature for 90 min. to give 0.6 g of 7a (21.5 %). M.p.: 176-7 °C (ethanol). $C_{12}H_{16}N_4O_4$ (280.28): Cal./found C, 51.42/51.69; H, 5.76/5.83; N, 19.99/19.84. Uv (96 % ethanol): λ_{max}(e) = 247 (0.239), 365 (0.461) nm. Ir (KBr): νNH: 3200, νC=O(acetyl): 1710, νC=O(ester): 1690, amide-I: 1675 cm^{-1}. ^{1}H-nmr (δ, $CDCl_3$): CH_3(Et), t(3H): 1.38 (J: 7 Hz), CH_3(4-acetyl), s(3H): 2.30, H-5; dd+t(2x1H): 2.54 (J: 17 and 9 Hz) and 2.64 (J: 17 Hz), H-4a, m(1H): 3.28, NCH_3(1), s(3H): 3.49, H-4, d(1H): 4.25 (J: 6 Hz), OCH_2 m (AB part of an ABX_3-type spin system, 2H): 4.35, NH(7), broad s(1H): 8.75 ppm. ^{13}C-nmr (δ, $CDCl_3$): CH_3(Et): 14.3, C-5: 28.8, CH_3(4-acetyl): 30.0, C-4a: 31.3, C-4: 40.2, NCH_3(1): 46.4, OCH_2: 62.0, C-3: 129.4, C-8a: 143.6, C=O(C-6 + ester): 163.5, 164.9, C=O(4-acetyl): 202.8 ppm.

Preparation of 3-^{14}C-6

Ethyl (1,3-^{14}C)-3-oxobutanoate was prepared from ethyl 1-^{14}C-acetate (30 mmol; 370 MBq) and purified as described[16] (exception: NaOH was used instead of NaOEt). Yield: 1.61 g (5.0 mmol) of Cu(II)-chelate complex. Specific activity: 21.53 MGq/mmol.

To the suspension of the ethyl acetoacetate Cu(II)-chelate complex (322 mg; 1.0 mmol) in ether (10 mL) 0.1 N HCl (20 mL) was added. After stirring for 1 h the organic layer was separated, the aqueous phase was extracted with 3x10 mL of ether, and after adding of NaCl (10 g) with an additional 10 mL. After workup to the residue 1c (418 mg; 2.0 mmol) water (5 mL) were added and after stirring for 2 h the mixture was allowed to stand overnight. On cooling yellow crystals precipitated to yield in 364 mg (1.13 mmol) of radiochemically pure 1,3-^{14}C-2c. M.p.: 119-20 °C. Specific activity: 10.98 MGq/mmol.

321 mg (1.0 mmol) of 1,3-^{14}C-2c was added to a solution of Na (30 mg) in 2-methoxyethanol (4.8 mL) and stirred for 1.5 h at 20 °C, then for 8 h at 80 °C. After cooling the mixture was diluted with water (2 mL) and the pH was adjusted with 1 N HCl to 6.5. The red solution was extracted with $CHCl_3$ (3x10 mL), the combined extract after drying was evaporated. The residue was chromatographed on silica gel using benzene-methanol 85:15 as eluent to give 20.7 mg (0.08 mmol) of radiochemically pure 3-^{14}C-6. M.p.: 212-14 °C.

REFERENCES

1. Studies on pyridazine compounds, XXIII. Part XXII: Kosáry, J.; Jerkovich, Gy.; Pólos, K.; Kasztreiner, E.; Magyar Kémiai Folyóirat (in Hungarian), 1986, 92, 459.
2. Druey, J.; Ringier, B. H.; Helv. Chim. Acta, 1951, 34, 195.
3. Salvadeo, A.; Villa, G.; Segagni, S.; Piazza, V.; Picardi, L.; Romano, M.; Parini, J.; Arzn. Forschung, 1985, 35, 623.
4. Szilágyi, G.; Kasztreiner, E.; Mátyus, P.; Kosáry, J.; Czakó, K.; Cseh, Gy.; Huszti, Zs.; Tardos, L.; Kósa, E.; Jaszlits, L.; Eur. J. Med. Chem., 1984, 19, 111.
5. Szilágyi, G.; Sóti, M.; Mátyus, P.; Kasztreiner, E.; Heterocycles, 1983, 20, 765.
6. LeCount, D. J.; Greer, A. T.; J. Chem. Soc. Perkin I., 1974, 297.
7. Morrison, Jr., R. W.; Mallory, W. R.; Styles, V. L.; J. Org. Chem., 1978, 43, 4844.
8. Mallory, W. R.; Morisson, Jr., R. W.; Styles, V. L.; J. Org. Chem., 1982, 47, 667.
9. Holly, S.; Sohár, P.; Theoretical and Technical Introduction to the series 'Absorption Spectra in the Infrared Region', (Ed.'s Láng, L.; Prichard, W. H.). Akadémiai Kiadó, Budapest, 1975. a) pp. 87, 111, 112.; b) p. 123.
10. Sohár, P.; Nuclear Magnetic Resonance Spectroscopy, CRC Press, Boca Raton, FL., 1983. a) Vol. 2, pp. 52, 181; b) Vol. 2, pp. 149, 173; c) Vol 2, pp. 25, 27; d) Vol. 1, p. 197.
11. All-Jallo, H. N.; Tetrahedron Lett., 1970, 875.
12. Jones, R. N.; Sándorfy, C.; The Application of Infrared and Raman Spectrometry to the Elucidation of Molecular Structure. (In the series 'Technique of Organic Chemistry', Ed. Weissberger, A.); Interscience, New York, 1956. Vol. 9, p. 459.
13. Karplus, M.; J. Chem. Phys., 1959, 30, 11; ibid, 1960, 33, 1842.
14. Pegg, D. T.; Doddrell, D. M.; Bendall, M. R.; J. Chem. Phys., 1982, 77, 2745.
15. Bendall, M. R.; Doddrell, D. M.; Pegg, D. T.; Hull, W. E.; High Resolution Multipulse NMR Spectrum Editing and DEPT. Bruker, Karlsruhe, 1982.
16. Figge, K.; Voss, H. P.; J. Labelled Compds., 1973, 9, 23.