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Bicyclic [*b*]-Heteroannulated Pyridazine Derivatives. 10. Acid Cleavage of Some β-Keto Esters in the Reaction with 4,4-Dimethyl- and 4-Phenyltetrahydropyridazine-3,6-dione 3-Hydrazones

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4,4-Dimethyltetrahydropyridazine-3,6-dione 3-hydrazone (**1**) reacted with β-keto esters in refluxing ethanol to give the acid cleavage products: 7,8-dihydro-3,8,8-trimethyltriazolo[4,3-*b*]pyridazin-6(5*H*)-one (**7**) and esters **9**. The yield of the reaction in most cases was nearly quantitative. At room temperature mostly the simple condensation products **4** were isolated. In analogous reactions, 4-phenyltetrahydropyridazine-3,6-dione 3-hydrazone (**2**) was found to be much less reactive. The hydrazone-ester condensation products **4** and some **5** were converted into the corresponding pyrazolylpyridazine derivatives **10** and **11**, respectively, by heating above their melting points; the formation of **7** was noted in the reactions with **4**. The results support the concept of different tautomeric preferences in **1** and **2**.

Key words: β-keto esters, acid cleavage, pyridazine-3,6-dione 3-hydrazone

The 4-substituted tetrahydropyridazine-3,6-dione 3-hydrazones, readily available in the reaction of the appropriately 3-substituted 3-cyanopropionic esters with hydrazine hydrate [1], have been found earlier to be interesting and versatile starting materials in the synthesis of bicyclic structures. Thus, the triazolo[4,3-*b*]pyridazine core was formed in the reactions with acetic and trifluoroacetic acids [2], whereas a number of pyridazino[6,1-*c*]triazine derivatives were obtained in those with α-keto esters [3]. In both cases the intermediate acylation or condensation products underwent a spontaneous or forced intramolecular cyclocondensation *via* the N2 pyridazine atom. A different cyclocondensation pattern, namely the formation of pyrazolylpyridazine derivatives by the attack on the exocyclic nitrogen atom, was the case in the reactions of 4-aryltetrahydropyridazine-3,6-dione 3-hydrazones with ethyl acetoacetate [3]. In the reactions with esters of dicarboxylic keto acids with the carbonyl function in an α position to one and β or γ to the other ester group, the cyclocondensation pathway depended mostly on the substituents in the starting

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hydrazone, *i.e.*, 4,4-dimethyl (as in **1**) *vs.* 4-phenyl (as in **2**) [4]. This suggests that the character of the substituent in position 4 has an important influence on the tautomeric equilibrium of the hydrazone-ketone condensation product.

Presently, studies on the reactions of two model hydrazones (**1** and **2**) with esters of dicarboxylic keto acids were extended to cover at first two β,γ- and β,δ-keto diesters, namely diethyl acetylsuccinate (**3a**) and diethyl 2-acetylglutarate (**3b**). Moreover, considering the observed distinction in the reactivity of **1** and **2**, the reactions of these compounds with acetoacetic ester (**3c**) and its 2-methyl and 2,2-dimethyl homologues (**3d** and **3e**, respectively) were investigated next. It was also expected that the alkoxycarbonyl- or alkoxycarbonylmethyl-substituted bicyclic reaction products may be useful intermediates in the synthesis of potentially bioactive compounds.

RESULTS AND DISCUSSION

The reactions of **1** with **3a** and **3b**, irrespective of the conditions applied (in an ethanol solution or with a large excess of the ester reagent and no additional solvent; room temperature in either case), did not stop at the condensation stage and give the corresponding **4**, but spontaneously continued *via* the supposed intermediate **6** to finally form 7,8-dihydro-3,8,8-trimethyltriazolo[4,3-*b*]pyridazin-6(5*H*)-one (**7**) in almost quantitative yields. A GC-MS analysis of the crude reaction mixtures revealed a high content of diethyl succinate and diethyl glutarate, respectively. This means that the reaction of **1** with **3a** and **3b** follows the mechanism of the acid cleavage of β-keto esters. The acetyl group departs from the ester and acetylates **1** with a simultaneous closure of the triazole ring (Scheme). In that respect the investigated reaction is analogous to that observed with 1,2-diaminobenzene [5], though it proceeds under much milder conditions.

In the case of **2**, the reaction with diethyl acetylsuccinate carried out in refluxing ethanol yielded only 24% of 7,8-dihydro-3-methyl-8-phenyltriazolo[4,3-*b*]pyridazin-6(5*H*)-one (**8**) and 55% of **5a**. Similar results were obtained in the analogous reaction of **2** with diethyl 2-acetylglutarate (11% of **8** and 65% of **5b**).

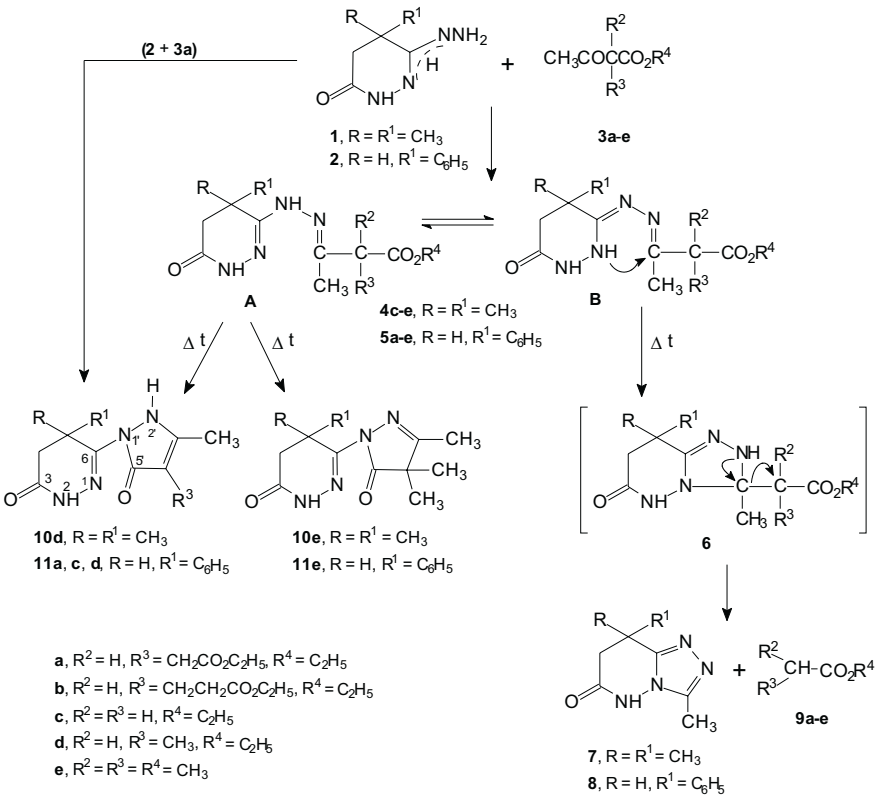
The above results support the earlier assumption that the tautomerism of **4** and **5** (**A** *vs.* **B** as shown in the Scheme) may be responsible for the different reactivity of the intermediates derived from **1** and **2**. In the case of **5**, contrary to that of **4**, the form with exocyclic NH (**A**) appears to be the major tautomer, formally incapable of yielding a bicyclic structure. Even prolonged reaction time (refluxing over 28 hours) shifted the equilibrium point to a limited extent only.

The acid cleavage of β-keto esters in the reaction with **1**, but not with **2** [4], was also observed with other derivatives of the acetoacetic esters. Thus, prolonged heating of **1** with ethyl acetoacetate (**3c**) and ethyl 2-methylacetoacetate (**3d**) in ethanol produced **7** in excellent yields (>85%). An analogous reaction with methyl 2,2-dimethylacetoacetate (**3e**) yielded only 70% of **7**, while column chromatography

made it possible to isolate the minor reaction product (15% yield). The latter was identified later as 6-(3,4,4-trimethyl-5-oxo-4,5-dihydropyrazol-1-yl)-5,5-dimethyl-4,5-dihydro-2*H*-pyridazin-3-one (**10e**) formed by intramolecular cyclocondensation of the intermediate **4e**. In all these reactions, GC-MS analysis of the reaction mixtures revealed presence of the corresponding acid cleavage products **9**. No simple condensation products **4** were isolated in the reactions of **1** with **3c–e** carried out at elevated temperature and in the presence of a protic solvent. However, when the reactions were run at room temperature with a considerable excess of the ester reagent and no other solvent, the corresponding 3-(pyridazinohydrazono)butyric esters **4c–e** were obtained in high yields.

The condensation of **2** with ethyl acetoacetate (**3c**) in refluxing ethanol, which yielded 92% of **5c**, has been reported earlier [3]. Under analogous conditions **2** and **3e** gave **5e** in 64% yield. In the reaction with ethyl 2-methylacetoacetate (**3d**), the expected condensation product (**5d**, 45%) was accompanied by a corresponding pyrazolylpyridazine derivative (**11d**, 8%), a product of the cyclocondensation of **5d**. No formation of **8** was noted in those reactions.

Scheme



In the ^{1}H and ^{13}C NMR spectra of most **4** and **5** some signals were split, thus indicating presence of two isomeric species, presumably the geometric isomers on the C=N bond formed in the condensation reaction. No attempts were made to resolve the mixtures or to determine the configuration of the predominant isomer.

Since in most cases, except those of the reactions of **1** with **3a** and **3b**, the formation of **7** and **8** required prolonged refluxing in ethanol, transformation of **4** and **5** at elevated temperatures was investigated next. When heated above the melting point, usually at 140–180°C, **4c–e** underwent an intramolecular cyclization, which followed two different pathways. One of them involved elimination of ethanol (methanol) with the formation of compounds **10d–e**, respectively. The other one led to the formation of **7** in accord with the acid cleavage mechanism (Scheme). Column chromatography of the reaction products was used to separate **10d–e** from **7**. Only **7** was obtained in the reaction with **4c**. An analogous thermal treatment of **5** gave in most cases intractable mixtures of several decomposition products; only **5c** and **5e** gave **11c** and **11e**, respectively, in moderate yields. The cyclization reactions are particularly smooth with **4e** and **5e**, that is with compounds in which there are no hydrogen atoms at the carbon atom next to the ester function. In the corresponding products (**10e** and **11e**, respectively), the formed pyrazole ring has a 4,5-dihydro structure in contradistinction to a 2,5-dihydro structure observed in the other **10** and **11** (Scheme).

Considering the possible tautomerism of **4** and **5**, the observed intramolecular cyclizations of these compounds with elimination of an alcohol molecule could have occurred either *via* N2 of the pyridazine moiety with the formation of a pyridazinotriazepine or *via* the hydrazine nitrogen atom with the formation of a 5-membered ring not fused with the pyridazine. In the earlier reports on similar cyclocondensations in various nitrogen heterocycle series, the products were in most cases identified as the pyrazolyl-substituted heterocycles [6–9]. Nevertheless, the formation of a thiazolotriazepine system was reported to result from the reaction of ethyl acetoacetate with 2-hydrazinothiazole [10]. Since the informations derived from the NMR spectra did not allow to unequivocally elucidate the structure of compounds **10** and **11** and to decide whether they contain fused or isolated rings, a well developed monocrystal of **10e** was subjected to crystallographic analysis. The ORTEP drawing of 6-(3,4,4-trimethyl-5-oxo-4,5-dihydropyrazol-1-yl)-5,5-dimethyl-4,5-dihydro-2*H*-pyridazin-3-one (**10e**) is shown in Fig. 1. It is assumed that other isolated compounds **10** and **11** have an analogous structure.

In the folded pyridazine ring of **10e**, the nitrogen atoms and the sp^2-hybridized carbon atoms C3 and C6 define the main ring plane. With respect to this plane, the roughly planar pyrazolone moiety (screw chair conformation) is twisted by 76.9(1)°. Standard bond lengths and valence angles characterize both rings. An intermolecular N1-H11.....N2′ hydrogen bond joins two molecules of **10e** together.

The results evidence a significant difference in reactivity of **1** and **2**. In the reaction with α-acetyl-substituted dicarboxylic esters **1**, even at room temperature, gave high yields of the acid cleavage of the ester, whereas **2** required prolonged heating and the yields were rather low. An analogous dependence was noted in the reaction with

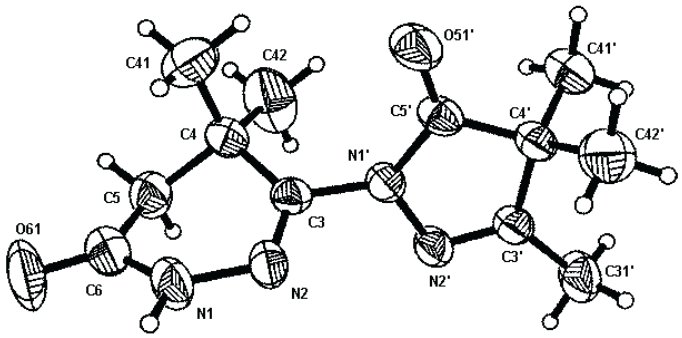


Figure 1. Molecular structure of **10e**.

acetoacetic ester and its 2-methyl and 2,2-dimethyl derivatives; acid cleavage was observed only in the reactions with **1**, whereas analogous reactions with **2** terminated in most cases in the formation of the condensation products **5**. Similarly, the acid cleavage products were isolated upon a relatively smooth thermal transformation of **4** above the melting point, while an analogous treatment of **5** resulted in rather complex mixtures.

EXPERIMENTAL

Melting points were determined in a Büchi apparatus and are reported uncorrected. The ^{1}H and ^{13}C NMR spectra were taken with Varian 400 MHz or Brucker DPX 400 MHz instruments with TMS as internal standard; two-dimensional and heteronuclear correlation (^{1}H, ^{13}C COSY) techniques were used wherever essential for proper signal assignments. Mass spectra were run on an AMD-604 Intectra GmbH instrument by routine electron ionization at 70 eV or, in the case of thermally unstable products, by the LSIMS method. Microanalyses were carried out on a Perkin-Elmer C-H-N analyzer. Merck DC-Alufolien with Kieselgel 60 F_{254} were used in the TLC purity monitoring. Column chromatography was performed on silicagel 60 Merck AG, granulation 0.063–0.200 mm, with chloroform gradually supplemented up to 10% with ethanol. Unless otherwise stated, all yield data refer to recrystallized, chromatographically homogeneous compounds with consistent elemental analysis results.

*Reactions of hydrazones **1** and **2** with keto esters **3**. General procedures*.

Procedure A. A solution or suspension of **1** or **2** (0.5–1.5 g) and the appropriate **3** (a 10–15% excess) in ethanol was heated for several hours under reflux. The crude reaction mixture was checked by GC-MS for the presence of the acid cleavage product and concentrated under reduced pressure to approximately 25% of the initial volume. The solid part, if any, was separated by filtration and the liquid was subjected to column chromatography. Detailed preparation data are given separately for individual compounds (**5a**, **5b**, **5e**, **7**, **8**, **10e**, **11a**).

Procedure B. **1** or **2** (0.5–1.5 g) was suspended in the appropriate **3** (a roughly 200% excess) and the mixture was stirred at room temperature until became homogeneous, in most cases several days. The crude reaction mixture was checked by GC-MS as in Procedure A. In order to remove the excess of **3**, the reaction mixture was washed 3–4 times by decantation with 10-mL portions of hexane and the residue was dissolved in chloroform, filtered if necessary, and subjected to column chromatography. Detailed preparation data are given separately for individual compounds (**5a**, **7**, **8**).

Procedure C. The reaction essentially was carried out as in Procedure B but washing with hexane, effected with vigorous stirring, left a crystalline product which was collected by filtration, checked for homogeneity (TLC) and analyzed with no further purification. Detailed preparation data are given separately for individual compounds (**4c–e**, **5d**, **11d**).

*Reactions of **1** with diethyl acetylsuccinate (**3a**) and with diethyl 2-acetylglutarate (**3b**).*

1 (1.12 g, 7.2 mmol) and 1.94 g of 95% **3a** (equivalent of 8.5 mmol) were made to react for 24 h in 40 mL of ethanol according to Procedure A. The GC-MS test for the presence of diethyl succinate was positive. The solid product obtained upon concentration of the mixture was recrystallized from acetonitrile to give 1.08 g (83%) of **7**.

An analogous reaction of 1.11 g (7.1 mmol) of **1** with 2.00 g (8.7 mmol) of **3b** in 40 mL of ethanol gave 0.88 g (68%) of **7**. Diethyl glutarate was detected in the reaction mixture.

The reactions of **1** with **3a** and **3b** carried out according to Procedure B also gave **7**. Only traces of the condensation products **4** were detected chromatographically.

3,8,8-Trimethyl-7,8-dihydro-[1,2,4]triazolo[4,3-b]pyridazin-6(5H)-one (7), colorless crystals, m.p. 177–180°C (MeCN). ^{1}H NMR ($CDCl_3$): δ 1.47 (s, 6H, 8-CH_3), 2.55 (s, 3H, 3-CH_3), 2.62 (s, 2H, CH_2), 12.21 ppm (br.s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 9.6 (3-CH_3), 25.7 (8-CH_3), 30.7 (C8), 41.2 (C7), 146.9 (C3), 151.6 (C8a), 169.8 ppm (C6). MS, *m/z* (% rel.int.): 180 (51.5%, M^+). Anal.: calcd. for $C_8H_{12}N_4O$ (180.21): C, 53.32; H, 6.71; N, 31.09. Found: C, 53.30; H, 6.53; N, 31.04.

*Reaction of **2** with diethyl acetylsuccinate.*

In accord with Procedure A, **2** (1.13 g, 5.5 mmol) and 1.52 g (6.7 mmol) of **3a** were refluxed in 80 mL of ethanol for 28 h. Diethyl succinate was detected by GC-MS. The solid product which precipitated on concentration was filtered to give 0.29 g (22.5%) of **8**. Column chromatography of the filtrate yielded 1.22 g (55%) of **5a** as the main reaction product. A small amount of **11a** (0.14 g, 7%) was isolated from the tail fractions.

When **2** (0.72 g, 3.5 mmol) and 4 mL of **3a** were made to react for 72 h according to Procedure B, only **5a** (1.30 g, 93%) was isolated by chromatography. Neither **8** nor **11a** were found to be formed in this experiment.

*3-Methyl-8-phenyl-7,8-dihydro-[1,2,4]triazolo[4,3-b]pyridazin-6(5H)-one (**8**),* colorless crystals, m.p. 249–252°C (EtOH); ^{1}H NMR ($CDCl_3$-CF_3COOH, 2:5): δ 2.81 (s, 3H, CH_3), 3.24–3.38 (m, 2H, CH_2), 4.80 (t, J = 8.1 Hz, 1H, CH), 7.26 (br.s, 2H, C_6H_5), 7.45 ppm (br.s, 3H, C_6H_5); ^{13}C NMR ($CDCl_3$-CF_3COOH, 2:5): δ 9.0 (CH_3), 32.5 (CH_2), 36.0 (CH), 128.28, 130.8, 131.0, and 134.0 (C_6H_5), 149.5 (C3), 149.9 (C8a), 171.9 ppm (CO). MS, *m/z* (% rel.int.): 228 (72%, M^+). Anal.: calcd. for $C_{18}H_{12}N_4O$ (228.25): C, 63.15; H, 5.30; N, 24.55. Found: C, 63.18; H, 5.28; N, 24.35.

*Diethyl 2-{1-[(6-oxo-4-phenyl-1,4,5,6-tetrahydropyridazin-3-yl)hydrazono]ethyl}butanedioate (**5a**),* a mixture of geometric isomers, m.p. 49–52°C. ^{1}H NMR ($CDCl_3$): δ 1.10, 1.16, 1.24, and 1.25 (4 × t, J = 7.2 Hz, 6H, $CH_2C\underline{H}_3$), 1.93 and 1.94 (2 × s, 3H, CCH_3), 2.55 and 2.64 (2 × dd, ^3J = 6.0 and 6.7 Hz, ^2J = 17.1 and 16.7 Hz, resp., 1H, C$\underline{H}$HCH), 2.70 (d, J = 16.7 Hz, 1H, endocyclic C$\underline{H}$H), 2.77–2.94 (m, 2H, CH$\underline{H}$CH and endocyclic CH$\underline{H}$), 3.61 and 3.66 (2 × dd, ^3J = 6.0 and 6.7 Hz, $^3{}'J$ = 8.5 and 8.0 Hz, resp.,1H, C$\underline{H}CH_2$), 3.89–4.16 (m, 4H, $C\underline{H}_2CH_3$), 4.81 and 4.83 (2 × d, J = 7.2 Hz, 1H, endocyclic CH), 7.24–7.31 (m, 5H, C_6H_5), 9.57 (br. s, `H, NH), 10.10 ppm (br. s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 14.0 and 14.1 ($CH_2\underline{C}H_3$), 16.1 and 16.2 (=$C\underline{C}H_3$), 32.3 and 32.6 (CH$\underline{C}H_2$), 33.6 and 34.0 (C5), 36.3 and 36.4 (C4), 49.8 and 50.0 ($\underline{C}HCH_2$), 60.7, 60.8, 61.0 and 61.2 ($\underline{C}H_2CH_3$), 127.2, 127.4, 127.6, 128.0, 128.2 and 137.1 (C_6H_5), 147.3 and 147.5 (=$\underline{C}CH_3$), 156.4 and 156.6 (C3), 167.0 and 167.2 (C6), 170.8, 171.0, 171.3 and 171.4 ppm (ester C=O). LSIMS, *m/z* (% rel.int.): 403 (100%, MH^+), 425 (12%, MNa^+). Anal.: calcd. for $C_{20}H_{26}N_4O_4$ (402.45): C, 59.69; H, 6.51; N, 13.92. Found: C, 59.38; H, 6.31; N, 13.78.

*Ethyl [3-methyl-5-oxo-1-(6-oxo-4-phenyl-1,4,5,6-tetrahydropyridazin-3-yl)-2,5-dihydro-1H-pyrazol-4-yl]-acetate (**11a**),* colorless crystals, m.p. 204–207°C (EtOH); ^{1}H NMR (CD_3OD): δ 1.20 (t, J = 7.2 Hz, 3H, $CH_2C\underline{H}_3$), 2.15 (s, 3H, CH_3), 2.62–3.16 (m, 2H, pyridazine CH_2), 3.23 (s, 2H, CH_2COO), 4.09 (q, J = 7.2 Hz, 2H, $C\underline{H}_2CH_3$), 5.61 (br. s, 1H, CH), 7.23–7.32 ppm (m, 5H, C_6H_5). MS, *m/z* (% rel.int.): 356 (100%, M^+). Anal.: calcd. for $C_{18}H_{20}N_4O_4$ (356.38): C, 60.66; H, 5.66; N, 15.72. Found: C, 60.45; H, 5.72; N, 15.57.

*Reaction of **2** with diethyl 2-acetylglutarate (**3b**).*

2 (1.05 g, 5.2 mmol) and 1.41 g (6.1 mmol) of **3b** were made to react for 28 h in 75 mL of ethanol according to Procedure A. The reaction mixture was worked up as above to yield 0.13 g (11%) of **8** and 1.40 g (65%) of **5b**. The corresponding analog of **11a** was not isolated.

*Diethyl 2-{1-[(6-oxo-4-phenyl-1,4,5,6-tetrahydropyridazin-3-yl)hydrazono]ethyl}pentanedioate (**5b**),* a mixture of geometric isomers obtained as a yellowish thick oil which was analyzed with no further purification. ^{1}H NMR ($CDCl_3$): δ 1.12 and 1.18–1.25 (t, *J* = 7.1 Hz and m, 6H, $CH_2C\underline{H}_3$), 1.85 (br.s, 3H, CH_3), 1.89–2.15 (m, 4H, CH_2CH_2), 2.70 and 2.71 (2 × dd, *J* = 1.4 and 16.8 Hz, 1H, endocyclic C<u>H</u>H), 2.92 and 2.94 (2 × dd, *J* = 1.4 and 16.8 Hz, 1H, endocyclic CH<u>H</u>), 3.17–3.21 (m, 1H, CC<u>H</u>CH_2), 3.88–3.96 and 4.01–4.16 (2 × m, 4H, unequivalent $OC\underline{H}_2CH_3$), 4.82 and 4.83 (2 × br.s, 1H, endocyclic CH), 7.22–7.31 (m, 5H, C_6H_5), 9.87 (br.s, 1H, NH), 10.60 ppm (br.s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 14.1, 14.2, and 14.3 ($OCH_2\underline{C}H_3$), 14.5 and 15.2 (=$C\underline{C}H_3$), 24.0 and 24.4 ($CH\underline{C}H_2CH_2$), 31.6 and 31.7 ($CHCH_2\underline{C}H_2$), 34.1 and 34.2 (C5), 36.4 and 36.6 (C4), 53.2 and 53.4 ($C\underline{C}HCH_2$), 60.4, 60.9, and 61.0 ($O\underline{C}H_2CH_3$), 127.2, 127.3, 127.4, 128.9, 137.7, and 137.8 (C_6H_5), 145.3 and 145.9 (N=$\underline{C}CH_3$), 155.7 (C3), 167.4 and 167.5 (C6), 171.6, 171.8, 172.8, and 172.9 ppm (ester C=O). LSIMS, *m/z* (% rel.int.): 417 (100%, MH^+). Anal.: calcd. for $C_{21}H_{28}N_4O_5$ (416.47): C, 60.56; H, 6.78; N, 13.45. Found: C, 60.32; H, 6.60; N, 13.27.

*Reactions of **1** with ethyl acetoacetate and its 2-methyl and 2,2-dimethyl homologues.*

The reactions carried out according to Procedure C gave high yields of the following products.

*Ethyl 3-[(4,4-dimethyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)hydrazono]butanoate (**4c**),* a roughly 1:1 mixture of geometric isomers, was obtained by stirring for 4 days the mixture of 1.0 g (6.4 mmol) of **1** and 5 mL of **3c**. Yield 1.55 g (90%) of pale yellow crystals, m.p. 114–117°C. ^{1}H NMR ($CDCl_3$): δ 1.24 and 1.28 (2 × t, *J* = 7.2 Hz, 3H, $OCH_2C\underline{H}_3$), 1.27 (s, 6H, 2 × CH_3CCH_3), 1.97 and 2.15 (2 × s, 3H, =CCH_3), 2.36 (2 × s, 2H, endocyclic CH_2), 3.37 and 3.43 (2 × s, 2H, =CCH_2), 4.14 and 4.19 ppm (2 × q, *J* = 7.2 Hz, 2H, $OC\underline{H}_2CH_3$). ^{13}C NMR ($CDCl_3$): δ 14.0 and 14.1 ($OCH_2\underline{C}H_3$), 15.0 (=$C\underline{C}H_3$), 24.0, 24.1 and 25.0 ($\underline{C}H_3C\underline{C}H_3$), 33.5 and 33.6 (C4), 39.1 (C5), 41.8 and 44.3 (=$C\underline{C}H_2$), 61.0 and 62.3 ($O\underline{C}H_2CH_3$), 147.5, 152.3 and 153.4 (C=N), 166.5 and 166.6 (C6), 168.9 and 169.8 ppm (ester C=O). LSIMS, *m/z* (% rel.int.): 269 (100%, MH^+), 291 (14%, MNa^+). Anal.: calcd. for $C_{12}H_{20}N_4O_3$ (268.31): C, 53.72; H, 7.51; N, 20.88. Found: C, 53.75; H, 7.40; N, 20.91.

*Ethyl 2-methyl-3-[(4,4-dimethyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)hydrazono]butanoate (**4d**)* was obtained by stirring for 16 days the mixture of 1.46 g (6.4 mmol) of **1** and 8 mL of **3d**. Yield 2.45 g (97%) of yellow crystals, m.p. 115–118°C. ^{1}H NMR ($CDCl_3$): δ 1.25 (t, *J* = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 1.31 (s, 6H, $C\underline{H}_3CC\underline{H}_3$), 1.38 (d, *J* = 7.3 Hz, 3H, $CHC\underline{H}_3$), 1.90 (s, 3H, =CCH_3), 2.39 (s, 2H, endocyclic CH_2), 3.62 (q, *J* = 7.3 Hz, 1H, C<u>H</u>CH_3), 4.16 ppm (q, *J* = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$). ^{13}C NMR ($CDCl_3$): δ 12.3 (=$C\underline{C}H_3$), 14.2 ($OCH_2\underline{C}H_3$), 14.8 ($CH\underline{C}H_3$), 24.1 and 24.2 ($\underline{C}H_3C\underline{C}H_3$), 33.6 (C4), 42.0 (C5), 48.4 ($\underline{C}HCH_3$), 61.0 ($O\underline{C}H_2CH_3$), 151.4 (=$\underline{C}CH_3$), 152.9 (C3), 166.7 (C6), 172.8 (ester C=O). LSIMS, *m/z* (% rel.int.): 283 (54.7%, MH^+). Anal.: calcd. for $C_{13}H_{22}N_4O_3$ (282.34): C, 55.30; H, 7.85; N, 19.84. Found: C, 54.97; H, 7.67; N, 19.94.

*Methyl 2,2-dimethyl-3-[(4,4-dimethyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)hydrazono]butanoate (**4e**)* was obtained from 1.02 g (6.6 mmol) of **1** and 6 mL of **3e**. Yield 1.77 g (95%) of yellow crystals, m.p. 119–121°C. ^{1}H NMR ($CDCl_3$): δ 1.33 (s, 6H, pyridazine CH_3CCH_3), 1.42 (s, 6H, chain CH_3CCH_3), 1.82 (s, 3H, =CCH_3), 2.39 (s, 2H, CH_2), 3.70 (s, 3H, OCH_3), 7.21 (br.s, 1H, NH), 8.79 ppm (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 12.7 (=$C\underline{C}H_3$), 23.4 (chain $\underline{C}H_3C\underline{C}H_3$), 24.3 (pyridazine $\underline{C}H_3C\underline{C}H_3$), 33.7 (C4), 42.3 (C5), 50.7 (chain $CH_3\underline{C}CH_3$), 52.3 (OCH_3), 152.5 (=$\underline{C}CH_3$), 154.6 (C3), 166.9 (C6), 175.8 ppm (ester C=O). LSIMS, *m/z* (% rel.int.): 283 (100%, MH^+), 305 (14%, MNa^+). Anal.: calcd. for $C_{13}H_{22}N_4O_3$ (282.34): C, 55.30; H, 7.85; N, 19.84. Found: C, 55.27; H, 7.69; N, 19.82.

Reactions carried out according to Procedure A (50 mL of ethanol, reaction time 30 h) gave either only or mostly **7**. Thus, 1.125 g (7.2 mmol) of **1** and 1.205 g (9.1 mmol) of **3c** afforded 1.078 g (83%) of **7**; 1.22 g (7.8 mmol) of **1** and 1.506 g (10.0 mmol) of **3d** afforded 1.22 g (86%) of **7**; 1.125 g (7.2 mmol) of **1** and 1.42 g (9.0 mmol) of **3e** afforded 0.927 g (71%) of **7**, separated by filtration upon concentrating the reaction mixture, and 0.272 g (15%) of **10e**, isolated by column chromatography.

*6-(3,4,4-Trimethyl-5-oxo-4,5-dihydropyrazol-1-yl)-5,5-dimethyl-4,5-dihydro-2H-pyridazin-3-one (**10e**),* colorless crystals m.p. 187–190°C (AcOEt). ^{1}H NMR ($CDCl_3$): δ 1.28 (s, 6H, CH_3CCH_3), 1.30 (s, 6 H, CH_3CCH_3), 2.05 (s, 3H, =CCH_3), 2.48 (s, 2H, CH_2), 8.56 ppm (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 13.3 (3′-CH_3), 20.9 (4′- or 5-$\underline{C}H_3C\underline{C}H_3$), 23.6 (4′- or 5-$\underline{C}H_3C\underline{C}H_3$), 34.8 (C4), 42.3 (C5), 48.6 (C4′), 149.5

(C6), 165.1 (C3′), 167.1 (C5′), 177.8 ppm (C3). MS, *m/z* (% rel.int.): 250 (100%, M^+). Anal.: calcd. for $C_{12}H_{18}N_4O_2$ (250.30): C, 57.58; H, 7.25; N, 22.38. Found: C, 57.56; H, 7.16; N, 22.42.

*Reaction of **2** with ethyl 2-methylacetoacetate (**3d**).*

2 (0.71 g, 3.5 mmol) and 4.5 mL of **3d** were made to react 4 weeks according to Procedure C. The main chromatographic fraction (0.52 g, 45% yield) was identified as **5d**, whereas a small amount (0.077 g, 8% yield) of the cyclization product **11d**, sparcely soluble in $CHCl_3$, was isolated from the tail fractions.

In another experiment, **2** (1.15 g, 5.6 mmol) and 1.5 mL of **3d** were refluxed with 40 mL of EtOH. After 5 h the mixture became homogeneous but another solid product began to separate. Ethanol (20 mL) was added and refluxing was continued for 20 h, the liquid was separated by decantation, the remaining solid was washed 4 times with 10-mL portions of ethanol, and the washings were combined with the main portion. Concentration of the liquid gave another portion of a solid which was identified as the cyclization product **11d**; its total yield was 0.7 g (43.5%). Column chromatography of the oil left upon removal of ethanol from the liquid part of the reaction mixture and the ethanol washings and filtrates yielded 0.62 g (33.5%) of **5d**.

*Ethyl 2-methyl-3-[(6-oxo-4-phenyl-1,4,5,6-tetrahydropyridazin-3-yl)hydrazono]butanoate (**5d**),* a mixture of stereoisomers as a colorless thick oil. ^{1}H NMR ($CDCl_3$): δ 1.12 and 1.20 (2 × t, *J* = 7.1 Hz, 3H, $CH_2C\underline{H}_3$), 1.23 and 1.24 (2 × d, *J* = 7.1 Hz, 3H, $CHC\underline{H}_3$), 1.84 and 1.85 (2 × s, 3H, $=CCH_3$), 2.70 and 2.71 (2 × dd, *J* = 1.8 and 16.8 Hz, 1H, endocyclic C<u>H</u>H), 2.91 and 2.93 (2 × dd, *J* = 7.8 and 16.8 Hz, 1H, endocyclic CH<u>H</u>), 3.27 and 3.28 (2 × q, *J* = 7.1 Hz, 1H, C<u>H</u>CH_3), 3.86–4.15 (m, 2H, unequivalent OCH_2), 4.82 and 4.83 (2 × dd, *J* = 7.8 and 1.8 Hz, 1H, endocyclic CH), 7.24–7.32 (m, 5H, C_6H_5), 9.75 (br.s, 1H, NH), 10.57 ppm (br.s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 14.1 and 14.2 ($CH_2\underline{C}H_3$), 14.3 and 14.7 ($CH\underline{C}H_3$), 14.4 and 14.8 ($=C\underline{C}H_3$), 34.1 (C5), 36.2 and 36.5 (C4), 48.4 and 48.5 ($\underline{C}HCH_3$), 60.7 and 60.8 ($\underline{C}H_2CH_3$), 127.3, 127.4, 128.9, 137.6, and 137.9 (C_6H_5), 147.2 and 147.8 (C3), 155.7 ($=\underline{C}CH_3$), 167.4 and 167.5 (C6), 172.8 and 173.1 ppm (ester C=O). LSIMS, *m/z* (% rel.int.): 331 (100%, MH^+), 353 (10.4%, MNa^+). Anal.: calcd. for $C_{17}H_{22}N_4O_3$ (330.38): C, 61.80; H, 6.71; N, 16.96. Found: C, 61.48; H, 6.53; N, 16.87.

*6-(3,4-Dimethyl-5-oxo-2,5-dihydropyrazol-1-yl)-5-phenyl-4,5-dihydro-2H-pyridazin-3-one (**11d**),* colorless crystals m.p. 259–263°C (MeOH). ^{1}H NMR ($CDCl_3$-CF_3COOH, 5:1): δ 2.00 (s, 3H, 4′-CH_3), 2.43 (s, 3H, 3′-CH_3), 3.10 (d, *J* = 18.0 Hz, 1H, 4-C<u>H</u>H), 3.47 (dd, *J* = 18.0 and 8.9 Hz, 1H, 4-CH<u>H</u>), 5.17 (d, *J* = 8.9 Hz, 1H, 5-CH), 7.21–7.26 (m, 2H, C_6H_5), 7.38–7.44 ppm (m, 3H, C_6H_5). ^{13}C NMR ($CDCl_3$-CF_3COOH, 5:1): δ 5.9 (4′-CH_3), 11.1 (3′-CH_3), 35.9 (C4), 39.4 (C5), 104.3 (C4′), 127.8, 131.1, 131.7, and 135.4 (C_6H_5), 146.9 (C6), 152.7 (C3′ or C5′), 157.2 (C3′ or C5′), 171.5 ppm (C3). MS, *m/z* (% rel.int.): 284 (100%, M^+). Anal.: calcd. for $C_{15}H_{16}N_4O_2$ (284.32): C, 63.37; H, 5.67; N, 19.71. Found: C, 63.27; H, 5.72; N, 19.73.

*Reaction of **2** with methyl 2,2-dimethylacetoacetate (**3e**).*

2 (2.03 g, 9.9 mmol) and 2.02 g (14.0 mmol) of **3e** were made to react for 72 h in 50 mL of methanol according to Procedure A. The crude product was separated by filtration and washed thrice with 10-mL portions of diethyl ether, next with 10 mL of hexane, and finally recrystallized from methanol to yield 2.26 g (69%) of **5e**.

*Methyl 2,2-dimethyl-3-[(6-oxo-4-phenyl-1,4,5,6-tetrahydropyridazin-3-yl)hydrazono]butanoate (**5e**),* colorless crystals m.p. 175–177°C (decompn.) from MeOH. ^{1}H NMR ($CDCl_3$): δ 1.24 and 1.38 (2 × s, 6H, CH_3CCH_3), 1.78 (s, 3H, $=CCH_3$), 2.71 (d, *J* = 16.6 Hz, 1H, 5-C<u>H</u>H), 2.94 (dd, *J* = 16.6 and 7.7 Hz, 1H, 5-CH<u>H</u>), 3.56 (s, 3H, OCH_3), 4.83 (d, *J* = 7.7 Hz, 1H, 4-CH), 7.22–7.32 (m, 5H, C_6H_5), 9.70 (br.s, 1H, NH), 10.55 ppm (br.s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 13.4 ($=C\underline{C}H_3$), 23.4 and 23.5 ($\underline{C}H_3C\underline{C}H_3$), 34.2 (C5), 36.5 (C4), 50.5 ($CH_3\underline{C}CH_3$), 52.1 (OCH_3), 127.2, 127.3, 128.9 and 137.8 (C_6H_5), 149.9 ($=\underline{C}CH_3$), 156.0 (C3), 167.3 (C6), 176.0 ppm (ester C=O). LSIMS, *m/z* (% rel.int.): 331 (36.2%, MH^+). Anal.: calcd. for $C_{17}H_{22}N_4O_3$ (330.38): C, 61.80; H, 6.71; N, 16.96. Found: C, 61.76; H, 6.62; N, 16.99.

*Pyrazolylpyridazines **10** and **11** by thermal cyclization of **4** and **5**.*

The appropriate **4** or **5** was heated without any solvent in an oil bath until evolution of the gaseous reaction products ceased. In order to separate and purify the reaction products the vitrous melt was subjected upon cooling to column chromatography. Alteratively, the melt was directly recrystallized from a suitable solvent. Detailed preparative data are given for individual compounds as follows.

4c (1.22 g, 4.5 mmol) heated for 1 h at 155–160°C yielded a lightly brown glassy melt which was dissolved in chloroform and subjected to chromatographic purification. Only **7** (0.72 g, 87%) was isolated as the tail fraction.

4d (1.455 g, 5.2 mmol) heated for 3 h at 140–175°C yielded 1.05 g of the melt which revealed (TLC) to be a mixture of products. Column chromatography gave 0.285 g (24%) of **10d** in the head fractions and 0.641 g (68%) of **7** in the tail fractions.

*6-(3,4-Dimethyl-5-oxo-2,5-dihydro-1H-pyrazol-1-yl)-5,5-dimethyl-4,5-dihydro-2H-pyridazin-3-one (**10d**),* colorless crystals, m.p. 226–229°C (EtOH). ^{1}H NMR (CD_3OD): δ 1.25 (s, 6H, 5-CH_3), 1.80 (s, 3H, 3′- or 4′-CH_3), 2.15 (s, 3H, 3′- or 4′-CH_3), 2.49 ppm (s, 2H, CH_2). ^{13}C NMR (CD_3OD): δ 7.8 (3′- or 4′-CH_3), 12.5 (3′- or 4′-CH_3), 25.0 (5-CH_3), 37.6 (C5), 44.5 (C4), 102.1 (C4′), 151.1 (C3′), 152.8 (C6), 166.5 (C5′), 171.4 ppm (C3). MS, *m/z* (% rel.int.): 236 (100%, M^+). Anal.: calcd. for $C_{11}H_{16}N_4O_2$ (236.27): C, 55.92; H, 6.83; N, 23.71. Found: C, 55.98; H, 6.84; N, 23.41.

4e (1.20 g, 4.3 mmol) heated for 3 h at 140–165°C yielded 0.94 g of an orange glassy melt. Column chromatography afforded in the head fractions 0.58 g (54%) of **10e**, identical with that obtained in the reaction of **1** with **3e**, and in the tail fractions 0.24 g (30%) of **7**.

5c (1.56 g, 3.2 mmol) heated for 2 h at 160–180°C gave a light brown glassy melt. Column chromatography made it possible to isolate 0.32 g (37%) of **11c**, m.p. 210–213°C (EtOH), identical with the sample prepared earlier [3].

5e (0.68 g, 2.1 mmol) heated for 3 h at 170–200°C gave a yellow glassy melt which crystallized when dissolved in 30 mL of ethanol to yield 0.46 g (75%) of **11e**.

*6-(3,4,4-Trimethyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)-5-phenyl-4,5-dihydro-2H-pyridazin-3-one (**11e**),* slightly yellowish crystals m.p. 210–212°C (EtOH). ^{1}H NMR ($CDCl_3$): δ 1.16 (s, 3H, 4′-CH_3), 1.24 (s, 3H. 4′-CH_3), 2.08 (s, 3H, 3′-CH_3), 2.74 (d, J = 16.5 Hz, 1H, 5-C<u>H</u>H), 3.06 (dd, J = 16.5 Hz and 8.0 Hz, 1H, 5-CH<u>H</u>), 5.20–5.23 (m, 1H, 4-CH), 7.21–7.30 (m, 5H, C_6H_5), 8.85 ppm (br.s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 13.2 (3′-CH_3), 20.8 and 21.1 (<u>C</u>H_3C<u>C</u>H_3), 34.7 (C5), 37.5 (C4), 50.0 (C4′), 127.0, 127.8, 129.2 and 137.1 (C_6H_5), 145.4 (C3′), 165.7 (C6), 166.9 (C3), 176.8 ppm (C5′). MS, *m/z* (% rel.int.): 298 (100%, M^+). Anal.: calcd. for $C_{16}H_{18}N_4O_2$ (298.35): C, 64.41; H, 6.08; N, 18.78. Found: C, 64.56; H, 6.10; N, 18.76.

Crystal structure determination.

*Crystal data for **10e**:* $C_{12}H_{18}N_4O_2$; M_r = 250.30; orthorhombic; $Pna2_1$; a = 22.977(5), b = 9.826(2), c = 5.9850(10) Å; V = 1351.2(5) Å^3; z = 4; D_x = 1.230 g/cm^3; T = 293 K; λ(MoKα) = 0.71073 Å; μ = 0.087 mm^{-1}; F(000) = 536; final R = 0.0656 for 1668 observed reflections [$I > 2.0\ \sigma(I)$].

All measurements of the crystals with dimensions of 0.30 × 0.3 × 0.5 mm were performed on a Kuma4CCD κ-axis diffractometer with graphite-monochromated MoKα radiation within $3.5 < \Theta < 25.0°$ [h: –27: 27; k: –11: 11; l: –7: 6]. The data were corrected for Lorentz and polarization effects. No absorption correction was applied. Data reduction and analysis were carried out with the Kuma Diffraction (Wrocław) programs. The number of reflections measured totaled 10402, of which 2330 were unique ($R_{int.}$ = 0.068).

The structure was solved by direct methods [11] and refined using the SHELXL program [12]. The refinement was based on F^2. All hydrogen atoms were located from a differential map and refined in the riding model. Refinement was finished at R_1 = 0.0656, wR_2 = 0.1143 (with $w = 1/[\sigma^2(F_0^2) + (0.0381P^2]$ where $P = (F_0^2 + 2F_C^2)/3$, s = 1.06.

Crystallographic data (excluding structural factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 181756 (fax: +44(1223)336-0363; e-mail: deposit@ccdc.cam.ac.uk).

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