Chemoselectivity and Conformational Analysis of the Reaction of 2-Acetylcycloalkanones with Benzohydrazide: Synthesis and Reduction of 1-Aroylcycloalkapyrazole Derivatives

by **Constantinos A. Tsoleridis*, Julia Stephanidou-Stephanatou, Chara Zika, Minothora Pozarentzi,** and **Stephanos Alevizopoulos**

Department of Chemistry, Laboratory of Organic Chemistry, University of Thessaloniki, Thessaloniki, 54124, Macedonia, Greece (fax: +2310-997679; e-mail: tsolerid@chem.auth.gr)

From the reaction of 2-acetylcyclopentanone and 2-acetyl-2-methylcyclopentanone with benzohydrazide, the 1-benzoyl-6a-hydroxycyclopentapyrazole derivatives **2a** and **2b** were obtained as the only reaction products, whereas from the reaction of 2-acetylcyclohexanone an epimeric *cis/trans* mixture of the 2-benzoyl-3-hydroxy-2*H*-indazole derivative **3c** was formed. The dehydration of the isolated compounds **2a** and **3c**, as well as the $NaBH_4$ and $NaBH_3CN$ reduction products of **2a** were studied. The structural assignments of the compounds derived were established by analysis of their NMR spectra (^1H, ^{13}C, DEPT, COSY, NOESY, HETCOR C–H, and COLOC C–H). The chemoselectivity of the reactions of **1a** and **1c** with benzohydrazide was studied by conformational analysis with MM2 and semiempirical (AM1 and PM3) MO calculations.

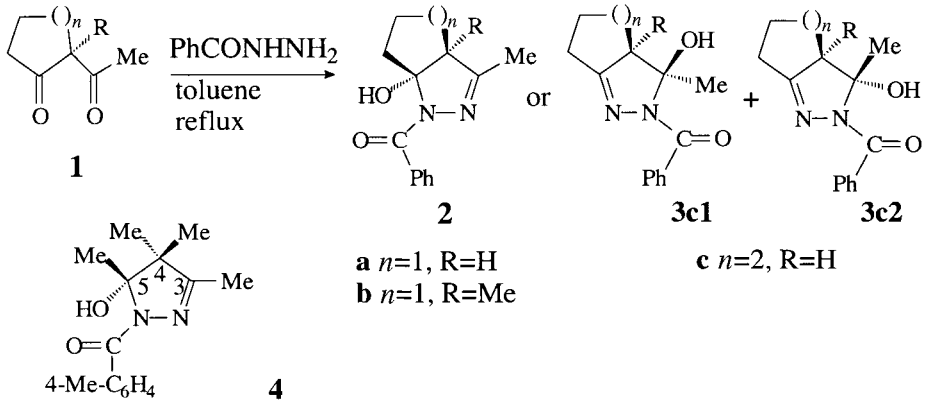
1. Introduction. – Pyrazoles are widely studied five-membered heterocyclic compounds because of their pharmacological, agrochemical, and analytical applications [1]. Pyrazole and pyrazolone rings when fused to carbocyclic rings are of interest in the chemical and pharmaceutical industry as herbicides [2] and analgesics [3]. These applications and the interesting chemoselectivity observed in the reactions of 2-acylcycloalkanones [4] with hydrazines [5], amines [6], and orthoformates [7] prompted us to devote our attention in the reaction of 2-acetylcyclopentanone and 2-acetylcyclohexanone with benzohydrazide, which can be used as convenient starting compounds for the chemoselective synthesis of fused pyrazoles.

2. Results and Discussion. – By refluxing 2-acetylcyclopentanone (**1a**) with benzohydrazide in toluene, only one product was isolated in 76% yield, which showed the presence of a OH group in the IR (3360 cm^{-1}) and also in the ^1H-NMR (5.20 ppm, D_2O exchangeable) spectra. Since, from the studied reaction, two possible OH isomers **2a** and **3a** can be formed, the structure of the isolated OH derivative was elucidated in connection with the spectral data of the known [8] 4,5-dihydro-5-hydroxy-3,4,4,5-tetramethyl-1-(4-methylbenzoyl)-1*H*-pyrazole (**4**) (*Scheme 1*). To the derived OH isomer, the structure of 1-benzoyl-1,3a,4,5,6,6a-hexahydro-6a-hydroxy-3-methylcyclopenta[*c*]pyrazole (**2a**) was assigned [9].

By analogy, from the reaction of 2-acetyl-2-methylcyclopentanone (**1b**) with benzohydrazide again only one OH derivative, the 1-benzoyl-1,3a,4,5,6,6a-hexahydro-6a-hydroxy-3,3a-dimethylcyclopenta[*c*]pyrazole (**2b**) was isolated in 67% yield.

Next, the reaction of 2-acetylcyclohexanone (**1c**) with benzohydrazide was studied, whereupon a mixture of two isomeric alcohols **3c** in a ratio of 3:1 was isolated in 80%

Scheme 1. *Condensation of β-Diketones* **1** *with Benzohydrazide*



yield. Recrystallization of the isomeric mixture from Et_2O/petroleum ether altered the ratio to 15 : 1, so that the chemical shifts of the major isomer could be extracted.

Assignments of the signals were achieved by use of 2D NMR spectroscopy (*Table 1*). Regarding the major isomer, COLOC correlations between the Me H-atoms appearing at δ 1.93 and also between the OH H-atom (δ 5.09) with the C-atoms resonating at 56.1 and 91.6 ppm were found. Moreover, the quaternary C-atom at 161.1 ppm correlates with the H-atoms at δ 2.61 – 2.70 and 1.90 – 2.10 and/or 1.88 – 2.05. The chemical shift of the Me C-atom at 27.4 ppm is quite different from that observed for the Me C-atom (14.8 ppm) of compound **2a**, but is in better agreement [9] with the Me–C(5) chemical shift (21.7 ppm) of compound **4**. In addition, the hydroxylated C-atom resonates at 91.6 ppm, a value that is closer to the one observed for C(5) (95.2 ppm) of compound **4** instead to that for C(6a) (103.0 ppm) of compound **2a**. The above COLOC data are in favor of structure **3c1**. From the contour plot of the COSY H,H map the sequence of the cyclohexyl CH_2 groups was extracted by using as starting point the H-atom at δ 2.65 – 2.77 at the bridgehead C-atom at 56.1 ppm with fixed axial orientation. In an analogous manner, the ^{13}C sequence of the minor isomer was accomplished (*Table 1*).

From the very similar chemical shifts observed for the H- and C-atoms of the two isomers, it can be concluded that they are *cis/trans* isomers, differing on the configuration at C(3), the fused cyclohexane ring being *cis* either to the OH or to the Me group. To distinguish between the two epimers, we compared the chemical shifts of the *Me*–C(3) C-atoms. It is obvious that, in the minor isomer, the Me group is crowded. This can result when the Me group is in the *endo*-configuration *cis* to C(4), so the structure **3c2** was assigned to the minor isomer. This conclusion is also supported by the ^{13}C-NMR chemical shifts of the model compounds, *cis*- and *trans*-2-methylcyclopentanols (**9a** and **9b**, resp.) and *cis*- and *trans*-1,2-dimethylcyclopentanes (**10a** and **10b**, resp.) [10] (c.f. *Scheme 4*). The data for **9a** and **10a** indicate that the Me C-atom is shielded more from the *cis*-OH than the *cis*-Me group in accordance with our results, where the C(4) resonates at 25.1 and 27.6 ppm for the major and the minor isomer, respectively. The proposed structure **3c** was also supported by the mass-spectrum fragmentation pattern, where a strong Ac fission $[M-43]^+$ was observed.

Table 1. *^{1}H-, ^{13}C-, and COLOC C–H-NMR Data*[a]) *for Compounds* **3c1** *and* **3c2**.

C-Atom[b])	Major isomer **3c1**			Minor isomer **3c2**		
	C	H	COLOC[c])	C	H	COLOC[c])
C(3)	91.6			93.8		
Me–C(3)	27.4	1.93 (*s*, 3 H)	91.6, 56.1	21.9	1.80 (*s*, 3 H)	93.8, 56.1
C(3a)	56.1	2.65–2.77 (*m*, 1 H)		56.1	2.92–2.98 (*m*, 1 H)	
C(4)	25.1	1.65–1.77 (*m*, 1 H)		27.6	1.22–1.42 (*m*, 1 H)	
		1.88–2.05 (*m*, 1 H)	161.1		2.05–2.18 (*m*, 1 H)	
C(5)	23.9	1.37–1.47 (*m*, 1 H)		24.2	1.43–1.47 (*m*, 1 H)	
		1.85–1.95 (*m*, 1 H)			1.88–1.98 (*m*, 1 H)	
C(6)	25.9	1.30–1.42 (*m*, 1 H)		25.9	1.30–1.42 (*m*, 1 H)	
		1.90–2.10 (*m*, 1 H)	161.1		1.90–2.00 (*m*, 1 H)	
C(7)	27.8	2.12–2.23 (*m*, 1 H)		27.8	2.12–2.23 (*m*, 1 H)	
		2.61–2.70 (*m*, 1 H)	161.1		2.61–2.70 (*m*, 1 H)	161.5
C(7a)	161.1			161.5		
OH		5.09 (br. *s*, 1 H)	91.6, 56.1		5.31 (br. *s*, 1 H)	
C=O	169.0			168.2		
C(1′)	134.4			134.4		
C(2′)/C(6′)	129.7	7.82–7.86 (*m*, 2 H)	169.0, 131.0	129.6	7.82–7.86 (*m*, 2 H)	
C(3′)/C(5′)	127.5	7.35–7.47 (*m*, 2 H)		127.5	7.35–7.47 (*m*, 2 H)	
C(4′)	131.0	7.45–7.48 (*m*, 1 H)	129.7	130.9	7.45–7.48 (*m*, 1 H)	

[a]) δ in ppm, J in Hz. [b]) Primed numbers refer to the C-atoms of the Ph group. [c]) Long-range (^2J and ^3J) correlations between the H-atoms on the left and the C-atoms stated on this column.

As a continuation of this study, we looked at the dehydration of the cyclopenta- and cyclohexapyrazolols **2a** and **3c**. Dehydration of the *cis/trans* mixture of the cyclohexapyrazolol **3c** (*Scheme 2*) was possible either with $SOCl_2$ and pyridine leading to the indazole derivative **6a** in 92% yield, or by refluxing in acidic EtOH, whereupon the isomeric indazole **6b** was isolated in 86% yield. A 2:1 mixture **6a**/**6b** was formed when the mixture **3c** was refluxed in toluene for 2 h in the presence of TsOH.

Concerning the structure of **6b**, COLOC correlations between the Me group H-atoms at δ 2.54 and the C-atoms at 119.1 and 139.4 ppm were found proving that the second bridgehead C-atom at 153.8 ppm should form the C=N bond. For the assignment of the cyclohexane CH_2 groups we started with the most downfield signal at δ 2.66, which was attributed to the $CH_2(7)$ H-atoms with their C-atom resonating at 23.9 ppm (*Table 2*). In the isomer **6a**, the two downfield signals at 151.4 and 143.3 ppm were assigned to C(3) and C(7a), respectively. Accordingly, the ^{1}H-NMR *triplets* at δ 3.06 and 2.39 were identified as the $CH_2(7)$ and $CH_2(4)$ groups, respectively. It should also be noted that there is a chemical shift difference, $\Delta\delta \approx 0.4$ ppm, between the Me H-atoms of **6b** and **6a**, which can be justified by the vicinity of the Me group with the C=O (in **6b**), which prefers an *anti*-periplanar conformation to N(1), and also by the influence of the Ph group. Analogously, the same chemical-shift difference, $\Delta\delta \approx$ 0.4 ppm, was observed between the $CH_2(7)$ H-atoms of **6a** and **6b**. It is also worth mentioning that, as a result of the flexibility of the cyclohexane ring, there is no differentiation between axial and equatorial H-atoms of $CH_2(4)$ and $CH_2(7)$. Therefore, they give *triplets* with the same $J = 6.1$ Hz.

Scheme 2. *Dehydration of Compounds* **2a** *and* **3c**

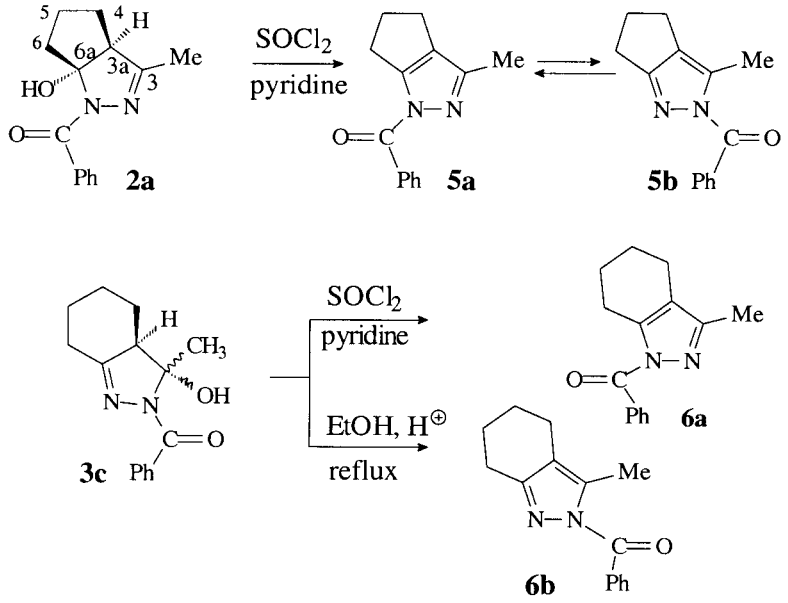


Table 2. *^{1}H, ^{13}C-, and COLOC C–H-NMR Data*[a]) *for Compounds* **6a** *and* **6b**

C-Atom[b])	Compound **6a**		Compound **6b**		
	C	H	C	H	COLOC[c])
C(3)	151.4		139.4		
Me–C(3)	12.0	2.18 (*s*, 3 H)	12.5	2.54 (*s*, 3 H)	139.4, 119.1
C(3a)	120.0		119.1		
C(4)	20.0	2.39 (*t*, *J* = 6.1, 2 H)	20.1	2.50 (*t*, *J* = 6.1, 2 H)	153.8, 139.4, 119.1
C(5)	22.2	1.70–1.86 (*m*, 2 H)	23.1	1.77–1.87 (*m*, 2 H)	119.1, 23.9, 20.1
C(6)	22.5	1.70–1.86 (*m*, 2 H)	23.0	1.73–1.83 (*m*, 2 H)	153.8, 20.1
C(7)	24.7	3.06 (*t*, *J* = 6.1, 2 H)	23.9	2.66 (*t*, *J* = 6.1, 2 H)	153.8, 23.1, 23.0
C(7a)	143.3		153.8		
C=O	167.7		168.7		
C(1′)	133.3		133.8		
C(2′)/C(6′)	131.1	8.00 (*d*, *J* = 8.5, 2 H)	131.2	7.93–7.97 (*m*, 2 H)	168.7, 132.2
C(3′)/C(5′)	127.6	7.41–7.46 (*m*, 2 H)	127.9	7.42–7.48 (*m*, 2 H)	133.8
C(4′)	132.0	7.50–7.55 (*m*, 1 H)	132.2	7.52–7.57 (*m*, 1 H)	131.2

[a]) δ in ppm, *J* in Hz. [b]) Primed numbers refer to the C-atoms of the Ph group. [c]) Long-range (^2J and ^3J) correlations between the H-atoms on the left and the C-atoms stated on this column.

Dehydration of the compound **2a** was possible with $SOCl_2$ and pyridine to give a tautomeric mixture **5a**/**5b** in a ratio of 3:1 (*Scheme 2*), whereas, by refluxing **2a** in toluene in the presence of a catalytic amount of TsOH, the isomeric ratio was changed to 10:1. To the major isomer, the structure of **5a** was assigned. The Me H-atoms resonating at δ 2.23, a value being analogous with the chemical shift of 2.18, observed for the Me H-atoms of compound **6a**, give COLOC correlations with the C-atoms at

131.0 and 148.7 ppm (*Table 3*). In addition, the CH_2(6) H-atoms correlate with C-atoms at 131.0 and 153.8 ppm indicating thus the C sequence in the pyrazole ring. It should also be pointed out that, compared to the chemical shift of C(6a) at 153.8 ppm of **5a**, the corresponding C-atom of **5b**, which forms a double bond with the N-atom resonates considerably downfield (166.0 ppm).

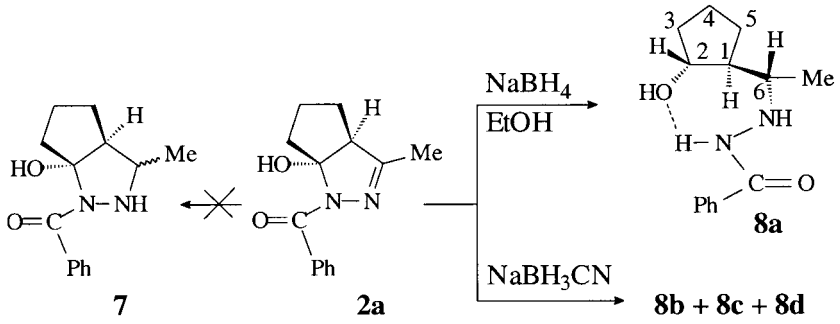
Table 3. *^{1}H, ^{13}C-, and COLOC C–H-NMR Data*[a]) *for Compounds* **5a** *and* **5b**

C-Atom[b])	Compound **5a**		COLOC[d])	Compound **5b**[c])	
	C	H		C	H
C(3)	148.7			136.8	
Me–C(3)	13.2	2.23 (*s*, 3 H)	148.7, 131.0	13.8	2.59 (*s*, 3 H)
C(3a)	131.0			129.0	
C(4)	22.2	2.55–2.61 (*m*, 2 H)	153.8, 131.0	21.9	2.55–2.61 (*m*, 2 H)
C(5)	30.3	2.55–2.61 (*m*, 2 H)		29.6	2.55–2.61 (*m*, 2 H)
C(6)	27.4	3.05–3.12 (*m*, 2 H)	153.8, 131.0	24.7	3.05–3.12 (*m*, 2 H)
C(6a)	153.8			166.0	
C=O	166.3			168.9	
C(1′)	132.3			134.1	
C(2′)/C(6′)	131.4	8.07–8.13 (*m*, 2 H)	166.3, 132.5	130.9	7.91–7.95 (*m*, 2 H)
C(3′)/C5′)	127.9	7.43–7.50 (*m*, 2 H)	132.3	127.8	7.20–7.55 (*m*, 2 H)
C(4′)	132.5	7.53–7.60 (*m*, 1 H)	131.4	132.0	7.20–7.55 (*m*, 1 H)

[a]) δ in ppm, *J* in Hz. [b]) Primed numbers refer to the C-atoms of the Ph group. [c]) Always as a mixture with **5a**. [d]) Long-range (^2J and ^3J) correlations between the H-atoms on the left and the C-atoms stated on this column.

In an attempt to study also the chemoselectivity of the completely saturated fused derivative **7**, the hydrogenation of the C=N bond of compound **2a** was attempted with $NaBH_4$ [11] in AcOH, whereupon, at room temperature, no reaction was observed, whereas, under reflux, many products were formed. Reduction was accomplished in 92% yield by stirring **2a** with $NaBH_4$ in EtOH at room temperature for 3 h to give, with ring cleavage, the *N*-(hydroxycyclopentyl)benzohydrazide **8a**, instead of the expected hydroxypyrazolidine **7**. This ring cleavage was found to be independent of the acidity of the EtOH soln., the amount of $NaBH_4$, and the temperature (−10 up to +25°) and, despite our considerable efforts with a variety of reaction conditions, we could not detect the desired product **7** (*Scheme 3*).

Scheme 3. *Reduction of Compound* **2a** *with $NaBH_4$ and $NaBH_3CN$*



Next, the reduction of **2a** with the more selective reagent $NaBH_3CN$ [12] was investigated, but, in this case, a mixture of three products, **8b**/**8c**/**8d**, in a ratio of 4:5:1 was formed. ^{13}C- and ^{1}H-NMR spectra (*Tables 4* and *5*), MS, and elemental analysis indicated that these three compounds, as well as compound **8a**, are stereoisomers. To

Table 4. *^{13}C-NMR Data for Compounds* **8a**–**8d**[a])

	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	6-Me	CO	C(1′)	C(2′)/C(6′)	C(3′)/C(5′)	C(4′)
8a	51.6	78.4	34.6	20.7	27.8	61.9	18.6	166.8	132.6	126.9	128.7	131.8
8b	50.3	72.4	34.2	22.2	27.1	57.0	19.0	168.3	132.5	127.0	128.8	132.1
8c	49.1	75.9	34.9	22.1	23.0	57.0	19.1	167.5	132.6	127.0	128.7	131.9
8d[b])	51.0	73.2	35.5	22.7	27.4	57.5	15.8	166.2	133.1	127.1	128.1	131.2

[a]) Primed numbers refer to the C-atoms of the Ph group. [b]) Solvent $CDCl_3$/(D_6)DMSO.

draw some conclusions about their stereochemical features, a series of 2D spectra (COSY, NOESY, HETCOR C–H, and COLOC C–H) were studied. For the configurational assignments of **8a**–**8d** the *cis*- and *trans*-2-methylcyclopentanols (**9a** and **9b**, resp.) were used as model compounds [10]. Comparing the ^{13}C chemical shifts of **9a** and **9b**, it is observed that in the *cis*-isomer a shielding is induced by the stereochemical interaction of the two substituents (*γ-gauche* effect). The relative shieldings for all C-atoms of **9a** are as follows: C(1), −4.6; C(2), −2.4; C(3), 0.6; C(4), 0.6, C(5), −0.8; C(6), −4.6 ppm (*Scheme 4*). The product **8a** showed for the hydroxylated C(2)-atom a chemical shift at 78.4 ppm with its CH at δ 4.07 observed as a *quadruplet* (J = 7.7 Hz). The relative downfield shifts for C(2) and C(6) of

Scheme 4. *Structures of Compounds* **8b**–**d** *and the Model Compounds* cis-*and* trans-*2-Methylcyclopentanol* (**9a** and **9b**, resp.) *and* cis- *and* trans-*1,2-dimethylcyclopentane* (**10a** and **10b**, resp.)

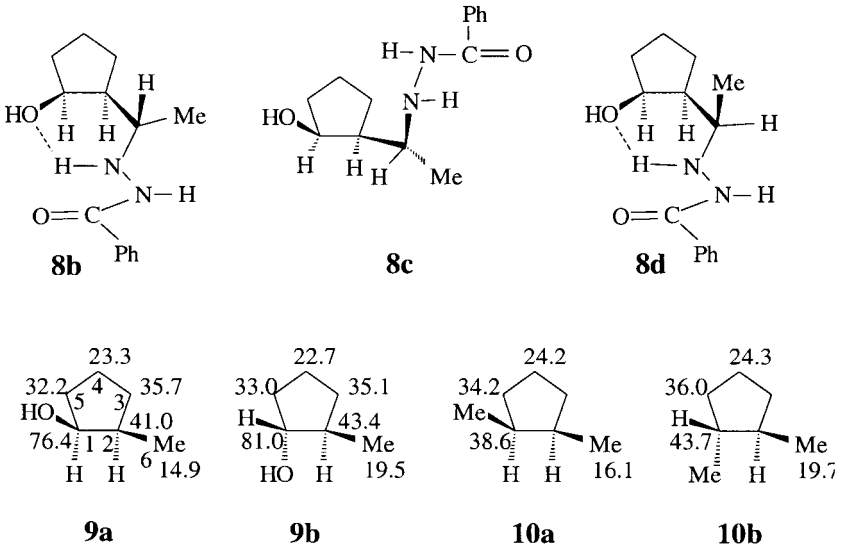


Table 5. *^{1}H-NMR Data*[a]) *of Compounds* **8a**–**8d**

H-Atom	**8a**	**8b**	**8c**	**8d**[b])
H–C(1)	1.59–1.77 (*m*)	1.54–1.70 (*m*)	1.75–1.80 (*m*)	1.80–2.00 (*m*)
H–C(2)	4.07 (*q*, *J* = 7.7)	4.48 (*dt*, *J* = 4.5, 2.2)	4.28–4.32 (*m*)	4.09 (*q*, *J* = 5.2)
H–C(3)	1.54–1.70 (*m*), 1.93–2.08 (*m*)	1.70–1.92 (*m*)	1.50–1.95 (*m*)	1.70–1.77 (*m*), 1.55–1.64 (*m*)
H–C(4)	1.45–1.59 (*m*), 1.65–1.77 (*m*)	1.51–1.62 (*m*)	1.50–1.95 (*m*)	1.55–1.64 (*m*), 1.70–1.77 (*m*)
H–C(5)	1.11–1.22 (*m*), 1.74–1.88 (*m*)	1.65–1.79 (*m*)	1.50–1.95 (*m*)	1.32–1.46 (*m*), 1.80–2.00 (*m*)
H–C(6)	2.86 (*dq*, *J* = 9.6, 6.4)	3.10 (*dq*, *J* = 9.3, 6.3)	3.38 (*dq*, *J* = 1.5, 6.4)	3.02 (*dq*, *J* = 5.9, 6.4)
Me–C(6)	1.12 (*d*, *J* = 6.4)	1.17 (*d*, *J* = 6.3)	1.21 (*d*, *J* = 6.4)	1.11 (*d*, *J* = 6.4)
OH[c])	4.60	3.80	4.33	4.32
NH[c])	9.00	8.15		9.82
H–C(2′)/H–C(6′)	7.78–7.83 (*m*, 2 H)	7.74–7.79 (*m*, 2 H)	7.80–7.82 (*m*, 2 H)	7.83–7.86 (*m*, 2 H)
H–C(3′)/H–C(5′)	7.38–7.45 (*m*, 2 H)	7.42–7.48 (*m*, 2 H)	7.40–7.45 (*m*, 2 H)	7.39–7.46 (*m*, 2 H)
H–C(4′)	7.47–7.53 (*m*, 1 H)	7.51–7.56 (*m*, 1 H)	7.49–7.54 (*m*, 1 H)	7.47–7.53 (*m*, 1 H)

[a]) δ in ppm, *J* in Hz. Primed numbers refer to the C-atoms of the Ph group. [b]) Solvent: $CDCl_3$/(D_6)DMSO. [c]) Always as a broad *singlet.*

compound **8a** indicate a *trans*-configuration of the cyclopentane ring substituents, as in the parent compound **2a**. From the spectral data given in *Tables 4* and *5*, and also from the analysis of the COSY and NOESY spectra, it was concluded that the structure of **8a** is the one depicted in *Scheme 3*.

The products **8b**–**8d** have a significant upfield shift for C(2) and C(6), and, in connection with the above data for compounds **9a** and **9b**, it can be concluded that the reduction with $NaBH_3CN$ affords products with *cis*-configuration with respect to C(1)–alkyl and C(2)–OH. Therefore, only two epimers can be formed by hydrogenation at C(3), either from *endo*- or from *exo*-position of the fused system.

The product **8b** showed for the C(2)-atom a chemical shift at 72.4 ppm with its CH H-atom at δ 4.48 observed as a *doublet* of *triplets* with $J_1 = 4.5$ Hz and $J_2 = 2.2$ Hz. In the NOESY spectrum, the Me H-atoms at δ 1.17 show a cross-peak with the H-atom at C(1), but there is no relationship with the rest of cyclopentane ring H-atoms suggesting that the Me group adopts an s-*trans* conformation with respect to C(2). Furthermore, the observed vicinal coupling magnitude between the H–C(1) and H–C(6) signals ($J = 9.3$ Hz) implies a *trans*-relationship for these two H-atoms, as depicted in *Scheme 4*. The configuration described favors the proximity of NH H-atom to the OH group forming thus a H-bond. The cyclopentane ring remains almost unaffected; therefore, the CH_2 H-atoms give overlapping *multiplets* in a very narrow chemical-shift region (1.50–1.90 ppm).

Compound **8c** shows for C(2) a chemical shift at 75.9 ppm, with its CH H-atom observed at δ 4.28–4.32 as a *multiplet*. This is the most downfield shift observed for the C(2) among the three products, indicating thus that this C-atom has the smallest interactions with the substituents at C(1). On the other hand, the most upfield shift for C(5) at 23.0 ppm reveals a possible interaction with the NHNHCOPh group, because

the chemical shift of the Me C-Atom is unaffected. The Me H-atoms appear as a *doublet* at δ 1.21 ($J = 6.4$ Hz) coupled with the H-atom at C(6), which appears as a *multiplet* at δ 3.38 (q, $J = 6.4$ Hz) with an additional very small coupling (*ca.* 1.5 Hz) with the H-atom at C(1), which, in turn, gives also a *multiplet* at δ 1.75 – 1.80. From the splitting patterns of these two *multiplets*, a *gauche* conformation could be proposed for the H–C(1) and H–C(6). The cyclopentane ring CH_2 H-atoms give overlapping *multiplets* in a very narrow chemical-shift region ($\delta = 1.50 - 1.95$) as a result of the small interactions with the substituents. The proposed structure **8c** is in good agreement with the above observations.

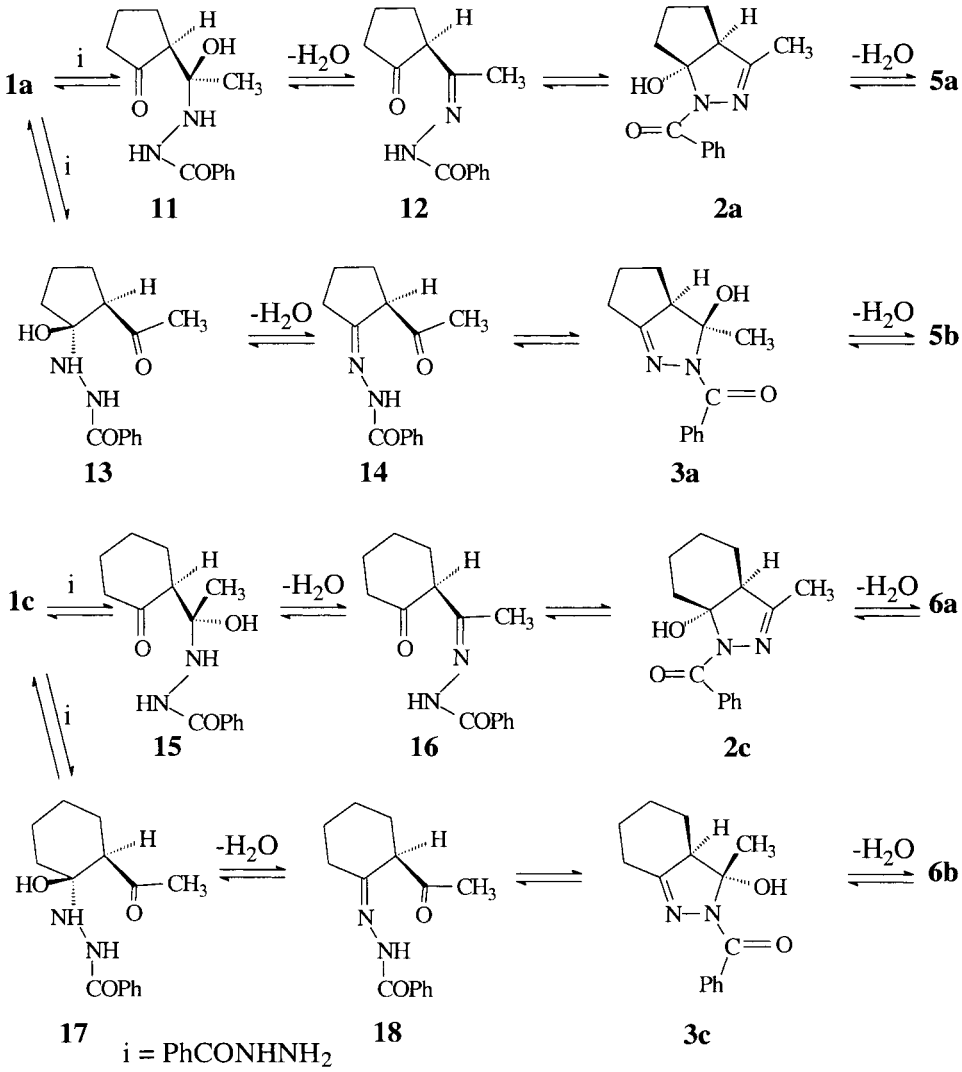
From the Me H-atom signal of **8d** at δ 1.11, which appears as a *doublet* with $J =$ 6.4 Hz, the H–C(6) at δ 3.02 was identified as a *doublet* of *quadruplets* ($J = 6.4$ and 5.9 Hz), and, consequently, the *multiplet* at δ 1.80 – 2.00 was assigned to H–C(1). From the splitting pattern of H–C(6), a *gauche* conformation can be suggested for H–C(1) and H–C(6). In addition, the H-atom at δ 4.09, which can readily be assigned to H–C(2) attached to the hydroxylated C-atom, shows COSY connectivities with the CH_2(3) H-atoms at δ 1.70 – 1.77 and δ 1.55 – 1.64. The Me H-atoms show a low-intensity COSY spot with H–C(1), revealing their *anti* conformation. In this case, a strong H-bond can be formed between the amine H-atom and the OH O-atom (six-membered ring), stabilizing this conformer and increasing the mutual influence of the rigid Me group to the cyclopentane H-atoms. Thus, the larger polarity (use of a droplet of (D_6)DMSO for NMR), the most downfield shift (9.82 ppm) for the NH and the most upfield shift (15.8 ppm) for the Me group can be explained. This interaction of the Me group causes the cyclopentane ring CH_2 H-atoms to give *multiplets* in a larger area compared with the isomers **8b** – **8c**.

Finally, as a result of the above analysis, it can be concluded that $NaBH_4$ reacts from the *endo*-position of the fused system, whereas the bulkier reagent $NaBH_3CN$ prefers the attack from the side of the OH group.

3. AM1-Computational Results. – A series of semiempirical quantum-chemical calculations (AM1 and PM3) [13][14] have been carried out in order to study the possible reaction pathways of benzohydrazide with the 1,3-diketones **1a** and **1c**. Although the semiempirical energy calculations do not refer to transition states, we have used the results as an estimation tool for the prediction of a favorable reaction pathway for the conversion of the 1,3-diketones **1a** and **1c** to the products **2a**, **2c**, and finally to **5a** and **5b**, or **6a** and **6b**, respectively. A general stepwise reaction scheme has been proposed for these transformations (*Scheme 5*). All structures are optimized first by molecular mechanics calculations MM2 (RMS GNORM < 0.1), and consequently by AM1 and PM3 at the RHF level (GNORM $= 0.001$). Both methods were used for comparison purposes. The configuration at C(2) of compounds **1a** – **1c** is the one depicted in *Scheme 1*. The amide C=O O-atom prefers the *anti*-conformation to the amide H-atom in intermediates **11** – **18,** and the *anti*-periplanar to the unsaturated N-atom in the fused compounds.

The energy profit of the *anti*- over the *syn*-periplanar conformation in the fused aromatics is calculated to be *ca.* 3 kcal/mol by both methods. Only the most stable (calculated by PM3) configuration between the OH group and the bridgehead H-atom is depicted in *Scheme 5*. The results are summarized in *Table 6* (AM1 and PM3). From

Scheme 5. *Stepwise Reaction of Benzohydrazide with Diketones* **1a** *and* **1c**. In the case of compounds **11**, **2a**, **13**, **3a**, **15**, **2c**, **17**, and **3c**, only the most-stable (PM3) *cis-trans* or *gauche-anti* configuration between the OH and the bridgehead H-atom is shown.



1a, initially the intermediates **11** or **13** can be formed with the same probability, assuming that reaction probabilities are analogous to the energy differences $\Delta\Delta H_f$ between the reactants and products. The formation of **12** and **14** by abstraction of H_2O has also the same probability. In *Table 6*, the experimental $\Delta H_f = -57.8$ kcal/mol of H_2O [15] was used in order to attain the net energy profit of the reaction. From intermediate **12**, compound **2a** can be formed having only the *cis*-configuration, since the energy profit for this transformation is calculated to be 12.07 kcal/mol. The *trans*-

Table 6. *Heats of Formation* (ΔH_f, [kcal/mol]) *Calculated for the Gaseous Phase* (AM1 and PM3) *for the Possible Intermediates in the Stepwise Reaction of PhCONHNH$_2$ with Diketones* **1a** *and* **1c**.

		Cyclopentane						Cyclohexane					
		ΔH_f		$\Delta\Delta H_f$[a])				ΔH_f		$\Delta\Delta H_f$		$\Delta\Delta$(C(5)–C(6))[b])	
		AM1	PM3	AM1	PM3			AM1	PM3	AM1	PM3	AM1	PM3
gauche[c])	**11**[d])	–73.98	–83.57	16.05	9.47	*gauche*	**15**[c])	–80.36	–86.90	16.28	9.93	–0.23	–0.46
anti		–72.06	–84.19	17.97	8.85	*anti*		–81.37	–84.65	15.27	12.18	2.7	–3.33
	12	–20.31	–25.99	53.67[f])	58.20[f])		**16**	–28.00	–30.77	53.37[f])	56.13[f])	0.3	2.07
				–4.13[g])	0.40[g])					–4.43[g])	–1.67[g])		
cis	**2a**	–16.42	–38.06	3.89	–12.07	*cis*	**2c**	–18.12	–36.56	9.88	–5.79	–5.99	–6.28
trans		14.92	–11.86	35.23	14.13	*trans*		–8.12	–25.91	19.88	4.86	15.35	9.27
anti	**5a**[h])	66.72	29.91	83.14[f])	67.97[f])	*anti*	**6a**[h])	42.68	15.30	60.80[f])	51.86[f])	22.34	16.11
				25.34[g])	10.17[g])					3.00[g])	–5.94[g])		
cis	**13**[d])	–80.45	–83.18	9.58	9.86	*cis*	**17**[c])	–88.50	–90.66	8.14	6.17	1.44	3.69
trans		–76.65	–85.22	13.38	7.82	*trans*		–88.28	–92.18	8.36	4.65	5.02	3.17
	14	–21.95	–26.31	58.50[f])	58.91[f])		**18**	–26.75	–28.81	61.75[f])	63.37[f])	–3.25	–4.46
				0.70[g])	1.11[g])					3.95[g])	5.57[g])		
cis	**3a**	–6.87	–28.79	15.08	–2.48	*cis*	**3c**	–23.17	–41.01	3.58	–12.20	11.50	9.72
trans		–7.47	–29.16	14.48	–2.85	*trans*		–22.69	–40.80	4.06	–11.99	10.42	9.14
anti	**5b**[h])	58.81	28.88	66.28[f])	58.04[c])	*anti*	**6b**[h])	41.72	15.26	64.89[f])	56.27[c])	1.39	1.77
				8.48[g])	0.24[d])					7.09[g])	–1.53[d])		

[a]) $\Delta\Delta H_f$ is the difference between the heat of formation of the products and reactants $\Delta\Delta H_f = \Delta H_f$(prod) – ΔH_f(rcact). [b]) $\Delta\Delta$(C(5)–C(6)) is equal to the difference $\Delta\Delta H_f$(cyclopentane derivative) – $\Delta\Delta H_f$(cyclohexane derivative). [c]) *gauche-anti* and *cis-trans* refer to the relative configuration between the OH and the bridgehead H-atom. [d]) $\Delta\Delta H_f$ is estimated for the conversion of compound **1a** ($\Delta H_f = -90.03$) to **11** or **13**. [e]) $\Delta\Delta H_f$ is estimated for the conversion of compound **1c** ($\Delta H_f = -96.64$) to **15** or **17**. [f]) $\Delta\Delta H_f$ is estimated for the conversion of the most-stable isomer. [g]) Adding the energy for the abstracted H_2O (ΔH_f (exper.) = –57.8 kcal/mol). [h]) Carbonyl O-atom is in *anti*-periplanar conformation relative to the unsaturated N-atom.

isomer, due to higher repulsions, has a higher energy by 26.2 kcal/mol than the *cis*-isomer. Transformation of **14** to **3a** has an energy profit of *ca.* 2.5–2.8 kcal/mol for both *cis*- and *trans*-epimers. The formation of **2a** over **3a** is more favorable by 9.2 kcal/mol (PM3) or by 10.6 kcal/mol (AM1), a result in agreement with the experimental observation that only **2a** was obtained.

Concerning the reaction of **1c**, the formation of **17** over **15** is slightly favored by 3.7–7.5 kcal/mol (PM3) and by 5.9–8.1 kcal/mol (AM1). The *trans*-**2c** has a higher energy by 10.6 kcal/mol (PM3) or 10.0 kcal/mol (AM1) over the *cis*-**2c**. Both epimers of **3c** have lower energy for the *cis*-**2c** by 6.2–6.4 kcal/mol (PM3) or by 5.8–6.3 kcal/mol (AM1). Since the reactions are amphidromous, this small energy difference can be the reason for the formation of **3c**. In *Table 6*, the last columns give the quantity $\Delta\Delta$(C(5)–C(6)) defined as the difference of $\Delta\Delta H_f$ (cyclopentane derivative) – $\Delta\Delta H_f$ (cyclohexane derivative). So, negative value means that in the corresponding transformation the cyclopentane derivative is the more favorable. The above calculated results are in good agreement with our experimental data, where no epimers **2c** and **3a** are obtained. By molecular-modeling studies, it was calculated that, in **1c**, the slightly favored (*ca.* 1 kcal/mol) arrangement of the Ac group is the one with its Me in *anti*-conformation to the CH H-atom of the cyclohexane ring and with the C=O O-atom away from the ring. In the intermediate **18**, the opposite conformation of the C=O O-atom is favored by *ca.* 0.6 kcal/mol. The epimer of **3c** depicted in *Scheme 5* corresponds

to the minor isomer **3c2**, although it is calculated to be a little more stable than **3c1** in the gaseous phase without solvent interactions.

Experimental Part

General. M.p.: *Kofler* hot-stage; uncorrected. Column chromatography (CC): *Merck* silica gel. Petroleum ether refers to the fraction boiling between 60 and 80°. IR Spectra: *Perkin-Elmer 297* spectrometer, in cm^{-1}. ^1H- and ^{13}C-NMR spectra: at 300 and 75 MHz, resp., on a *Bruker AM-300* spectrometer with $CDCl_3$ as solvent unless otherwise stated; the chemical shifts (δ) [ppm] relative to TMS (0 ppm) as internal standard for ^1H- and relative to $CDCl_3$ (77.05 ppm) for ^{13}C-NMR spectra, *J* in Hz; signal assignments were made by 2D homo- (COSY and NOESY) and heteronuclear (HETCOR and COLOC) shift-correlation spectra. EI-MS: *VG TS-250* instrument, in *m*/*z* (rel. int. %). Elemental analyses: *Perkin-Elmer 2400-II* CHN analyzer.

The minimum-energy conformation of each compound was computed with the AM1 and PM3 methods as implemented in the MOPAC package [16] version 6.3. All stationary points were refined by minimization of the gradient norm of the energy to at least 0.01 kcal/mol.

1-Benzoyl-1,3a,4,5,6,6a-hexahydro-6a-hydroxy-3-methyl-cyclopenta[c]pyrazole (**2a**). To a soln. of *2-acetylcyclopentanone* (**1a**; 1.26 g, 10 mmol) in toluene (50 ml), benzohydrazide (1.5 g, 11 mmol) was added, and the mixture was refluxed for 6 h using a *Dean-Stark* water trap. The solvent was removed, and the mixture was chromatographed (silica gel; petroleum ether/AcOEt 3:1) to give **2a** (1.85 g, 76%). White crystalline solid (Et_2O). M.p. 109–110°. IR (nujol): 3360, 1630. ^1H-NMR: 1.51–1.66 (*m*, 1 H–C(5)); 1.69–1.79 (*m*, 1 H–C(4)); 1.83–1.95 (*m*, 1 H–C(5)); 1.99 (*s*, Me); 2.04–2.24 (*m*, 1 H–C(4), 1 H–C(6)); 2.60–2.71 (*m*, 1 H–C(6)); 3.22–3.30 (*m*, 1 H–C(3a)); 5.20 (br. *s*, OH); 7.37–7.50 (*m*, 2 H_m, H_p); 7.86–7.90 (*m*, 2 H_o). ^{13}C-NMR: 14.8 (Me); 25.7 (C(5)); 29.6 (C(4)); 40.9 (C(6)); 59.7 (C(3a)); 103.0 (C(6a)); 127.7 (C_m); 129.8 (C_o); 134.1 (C_i); 131.2 (C_p); 159.0 (C(3)); 167.4 (C=O). MS: 244 (92, M^+), 227 (85), 105 (100). Anal. calc. for $C_{14}H_{16}N_2O_2$ (244.3): C 68.83, H 6.60, N 11.47; found: C 68.78, H 6.63, N 11.34.

2-Acetyl-2-methylcyclopentanone (**1b**). To a cooled suspension of NaH (1.5 g, 6 mmol) in DMSO (35 ml) **1a** (6 ml, 5 mmol) was added dropwise under cooling, and the mixture was stirred for a further 2 h. The excess of NaH was destroyed by careful addition of H_2O, and the org. material was extracted with CH_2Cl_2. The CH_2Cl_2 soln. was dried, and the solvent was evaporated to provide **1b** (3.5 g, 50%). Oil [17]. IR (neat): 1710, 1705. ^1H-NMR: 1.37 (*s*, Me–C(2)); 1.67–1.77 (*m*, 1 H–C(3)); 1.88–2.00 (*m*, 2 H–C(4)); 2.19 (*s*, MeCO); 2.30–2.37 (*m*, 2 H–C(5)); 2.56–2.67 (*m*, 1 H–C(3)). ^{13}C-NMR: 19.3; 20.3; 26.1; 34.0; 38.0; 63.7; 205.7; 216.8.

1-Benzoyl-1,3a,4,5,6,6a-hexahydro-6a-hydroxy-3,3a-dimethyl-cyclopenta[c]pyrazole (**2b**). To a soln. of **1b** (1.40 g, 10 mmol) in toluene (50 ml), benzohydrazide (1.5 g, 11 mmol) was added, and it was proceeded as described above to give, after CC (petroleum ether/AcOEt 7:1), **2b** (1.67 g, 67%). White solid (Et_2O/petroleum ether). M.p. 129–130°. IR (nujol): 3400, 1620. ^1H-NMR: 1.25 (*s*, Me–C(3a)); 1.32–1.47 (*m*, 1 H–C(5)); 1.62–1.80 (*m*, H–C(4), H–C(5)); 1.94 (*s*, Me–C(3)); 1.96–2.09 (*m*, 1 H–C(4), 1 H–C(6)); 2.75–2.82 (*m*, 1 H–C(6)); 5.32 (br. *s*, OH); 7.38–7.46 (*m*, 3 arom. H); 7.85–7.88 (*m*, 2 arom. H). ^{13}C-NMR: 12.3 (*Me*–C(3a)); 17.4 (*Me*–C(3)); 22.9 (C(5)); 38.2 (C(4)); 40.6 (C(6)); 60.4 (C(3a)); 101.1 (C(6a)); 127.6 (C_o); 129.8 (C_m); 131.0 (C_p); 134.2 (C_i); 162.3 (C(3)); 167.5 (C=O). Anal. calc. for $C_{15}H_{18}N_2O_2$ (258.3): C 69.74, H 7.02, N 10.84; found: C 69.91, H 7.09, N 11.01.

*2-Benzoyl-3,3a,4,5,6,7-hexahydro-3-hydroxy-3-methyl-2*H-*indazole* (**3c**). The reaction was carried out as described above to give, after CC, a 3:1 isomeric *cis/trans* mixture of **3c** in 80% yield. White solid. M.p. 102–104, and 129–130°. IR (nujol): 3260, 1630. ^1H- and ^{13}C-NMR: see *Table 1*. MS: 258 (93, M^+), 243 (38), 241 (86), 215 (84), 173 (99), 105 (100). Anal. calc. for $C_{15}H_{18}N_2O_2$ (258.3): C 69.74, H 7.02, N 10.84; found: C 69.63, H 6.89, N 11.06.

*1-Benzoyl-4,5,6,7-tetrahydro-3-methyl-1*H-*indazole* (**6a**). To a cooled soln. of the 3:1 isomeric *cis/trans* mixture of **3c** (1.3 g, 5 mmol) in dry toluene (30 ml), dry pyridine (1 ml) was added, followed by the dropwise addition of a $SOCl_2$ soln. (0.8 ml) in dry toluene (20 ml) at such a rate to maintain the temp. ~6°. After the end of the addition, the mixture was stirred at ambient temp. for 24 h. The mixture was filtered, washed with H_2O, and dried (Na_2SO_4). Removal of the solvent gave **6a** (1.11 g, 92%). White crystalline solid (Et_2O/petroleum ether): M.p. 91–92°. IR (nujol): 1670. ^1H- and ^{13}C-NMR: see *Table 2*. MS: 240 (75, M^+), 225 (5), 212 (9), 135 (85), 105 (100). Anal. calc. for $C_{15}H_{16}N_2O$ (240.3): C 74.97, H 6.71, N 11.66; found: C 74.81, H 6.86, N 11.50.

*2-Benzoyl-4,5,6,7-tetrahydro-3-methyl-2*H-*indazole* (**6b**). A soln. of the 3:1 isomeric *cis/trans* mixture of **3c** (0.26 g, 1 mmol) was refluxed in EtOH, containing a cat. amount of HCl, for 1 h. Upon cooling, **6b** was

crystallized (0.21 g, 86%). White solid. M.p. 125–126°. IR (nujol): 1690. ^{1}H- and ^{13}C-NMR: see *Table 2*. MS: 240 (94, M^+), 225 (15), 212 (37), 135 (100), 105 (84). Anal. calc. for $C_{15}H_{16}N_2O$ (240.3): C 74.97, H 6.71, N 11.66; found: C 74.99, H 6.68, N 11.59.

*1-Benzoyl-1,4,5,6-tetrahydro-3-methylcyclopenta[*c*]pyrazole* (**5a**) *and 2-Benzoyl-2,4,5,6-tetrahydro-3-methylcyclopenta[*c*]pyrazole* (**5b**). The dehydration procedure described above for the formation of **6a** with $SOCl_2$ and pyridine was followed to give a 3:1 mixture **5a**/**5b** in 95% yield. White crystalline solid. M.p. 44–46°. IR (nujol): 1670. ^{1}H- and ^{13}C-NMR: see *Table 3*. MS: 226 (21, M^+), 121 (12), 105 (100). Anal. calc. for $C_{14}H_{14}N_2O$ (226.3): C 74.31, H 6.24, N 12.38; found: C 74.18, H 6.32, N 12.50.

Reduction of **2a** *with* $NaBH_4$. A soln. of **2a** (0.24 g, 1 mmol) and $NaBH_4$ (0.08 g, 2 mmol) in EtOH (20 ml) was stirred at r.t. for 3 h. To the residue obtained from evaporation, H_2O was added (15 ml), and the mixture was extracted with CH_2Cl_2 (3 × 20 ml). The CH_2Cl_2 extract was dried (Na_2SO_4), evaporated, and the residue was recrystallized from EtOH to give *N′-[1-(2-hydroxycyclopentyl)ethyl]benzohydrazide* (**8a**, 0.23 g, 92%). White crystalline solid. M.p. 102–103°. IR (nujol): 3230, 1620. ^{1}H- and ^{13}C-NMR: see *Tables 4* and *5*. MS: 248 (49, M^+), 233 (30), 231 (17), 163 (78), 145 (48), 105 (100). Anal. calc. for $C_{14}H_{20}N_2O_2$ (248.3): C 67.71, H 8.12, N 11.28; found: C 67.66, H 8.17, N 11.38.

The reduction of **2a** with $NaBH_4$ was studied under various reaction conditions (lower temp., various molar ratio of reagents, different reaction times) with no change in the reaction product. However, when the solvent was changed from EtOH to AcOH, no reaction was observed at lower temp., whereas, under reflux, many products were formed. No reaction was observed, when EtOH/THF was used as solvent.

Reduction of **2a** *with* $NaBH_3CN$. To a soln. of **2a** (0.49 g, 20 mmol) in AcOH (5 ml) $NaBH_3CN$ (0.5 g, 8 mmol) was added under Ar. The mixture was stirred at r.t. for 10 h, then H_2O was added, and the aq. soln. was basified with 50% NaOH soln. and extracted with CH_2Cl_2. The org. phase was washed with H_2O, dried (Na_2SO_4), and evaporated under vacuum. The residue was chromatographed (silica gel; petroleum ether/AcOEt 2:1). Isomer **8b** was eluted first (0.1 g, 20%). White crystalline solid. M.p. 146–148°. IR (nujol): 3250, 3210, 1615. ^{1}H- and ^{13}C-NMR: see *Tables 4* and *5*. MS: 248 (14, M^+), 163 (59), 105 (100). Anal. calc. for $C_{14}H_{20}N_2O_2$ (248.3): C 67.71, H 8.12, N 11.28; found: C 67.77, H 8.10, N 11.34.

Isomer **8c** was eluted second (0.12 g, 24%) as a white crystalline solid: M.p. 105–107°. IR (nujol): 3380, 3260, 1620. ^{1}H- and ^{13}C-NMR: see *Tables 4* and *5*. MS: 248 (67, M^+), 231 (8), 163 (100), 105 (89). Anal. calc. for $C_{14}H_{20}N_2O_2$ (248.3): C 67.71, H 8.12, N 11.28; found: C 67.68, H 8.29, N 11.23.

Isomer **8d** was eluted third (0.025 g, 5%) as an oil, which was crystallized from EtOH as a white solid: M.p. 99–102°. IR (neat): 3380, 3370, 1630. ^{1}H- and ^{13}C-NMR: see *Tables 4* and *5*. MS: 248 (81, M^+), 231 (8), 163 (100), 105 (80). Anal. calc. for $C_{14}H_{20}N_2O_2$ (248.3): C 67.71, H 8.12, N 11.28; found: C 67.85, H 8.09, N 11.25.

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