ACYLATION OF GUANYLHYDRAZONES DERIVED FROM CYCLIC KETONES: SYNTHESIS OF 3-ACYLAMINO-1-CYCLOALKENYL-5-METHYL-1*H*-1,2,4-TRIAZOLES[#]

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Abstract - Reaction of guanylhydrazones derived from different cycloalkanones, 1-indanone and 4-chromanone, respectively, with excessive acetic anhydride leads to the formation of 3-acetylamino-1-cycloalkenyl-5-methyl-1*H*-1,2,4-triazoles. However, with camphor guanylhydrazone only the corresponding *N,N'*-diacetyl-guanylhydrazone was obtained, whereas 2-adamantone guanylhydrazone afforded 2-(3-acetylamino-5-methyl-1,2,4-triazol-1-yl)-2-adamantyl acetate. Detailed NMR spectroscopic studies (^{1}H, ^{13}C) with the title compounds and their guanylhydrazone precursors are presented.

Guanylhydrazones (alkylideneaminoguanidines, amidohydrazones, diaminomethylenehydrazones, *Chem. Abstr.*: 2-ylidenehydrazinecarboximidamides), produced by the acid-catalized reaction of aminoguanidine salts with oxo compounds, are known since the end of the last century[1] and represent a class of compounds with a wide variety of interesting biological activities.[2,3] Moreover, they are also used as precursors in the construction of polyfunctional nitrogen heterocycles.[4] Thus, for instance, we recently reported the tranformation of guanylhydrazones derived from aromatic aldehydes into 3-acylamino-5-aryl-1,4-diacyl-4,5-dihydro-1,2,4-triazoles[5] as well as the cyclisation of acylated N^{1}-(glycopyranosylamino)-guanidines to 3-amino-N^{1}-glycopyranosyl-5-methyl-1,2,4-triazoles.[6] In continuation of our studies[5-8] concerning the chemistry and spectroscopic properties of guanylhydrazones we investigated the reaction of

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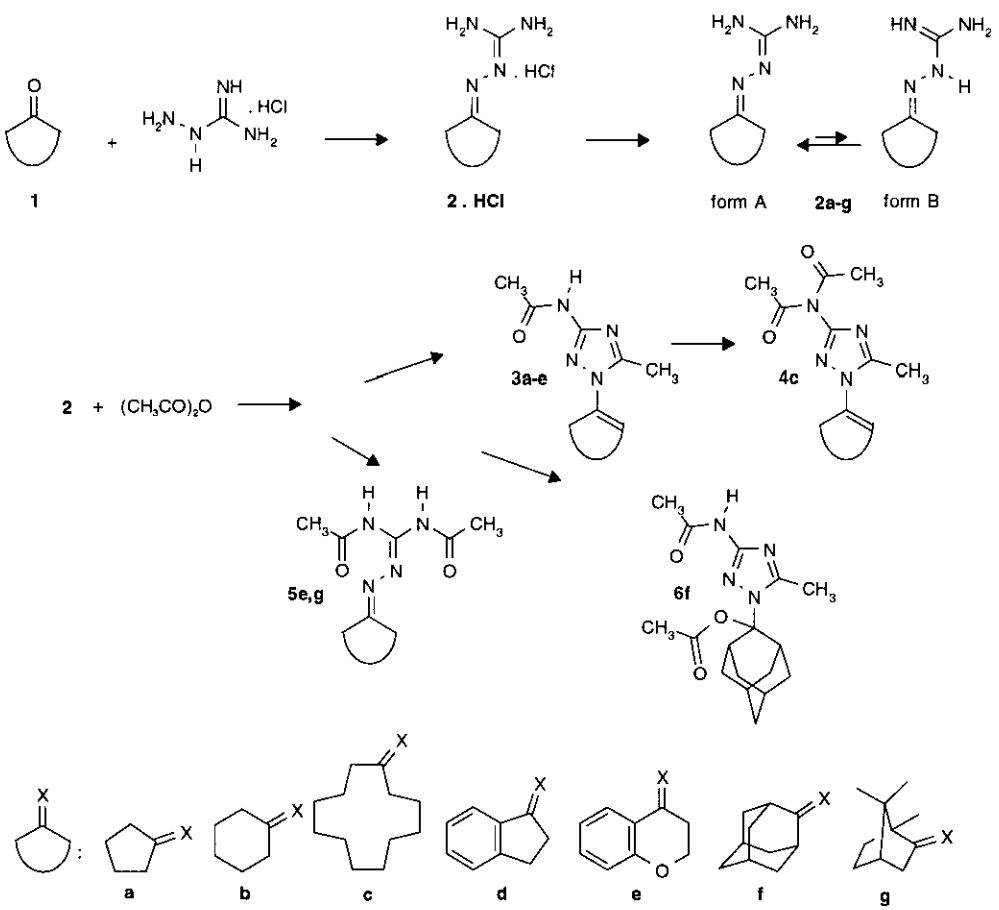
[#] *Dedicated with best personal wishes to Prof. Dr. Gottfried Heinisch on the occasion of his 60th anniversary*

guanylhydrazones derived from cyclic ketones with acetic anhydride in order to gain a suitable access to correspondingly N^1-substituted 3-amino-5-methyl-1,2,4-triazoles.

Chemistry

The synthesis of compounds (**2**) - (**8**) is outlined in Schemes 1 and 2, respectively. Reaction of cyclic ketones (**1**) with aminoguanidine hydrochloride, as specified in the Experimental, provided an efficient method for the synthesis of the hydrochloride salts of hydrazones (**2**), from which the corresponding free bases were obtained by treatment of **2•HCl** with strong bases. The reaction of guanylhydrazones (**2**) with excessive acetic anhydride at 100 °C led to a non-uniform palette of products (Scheme 1).

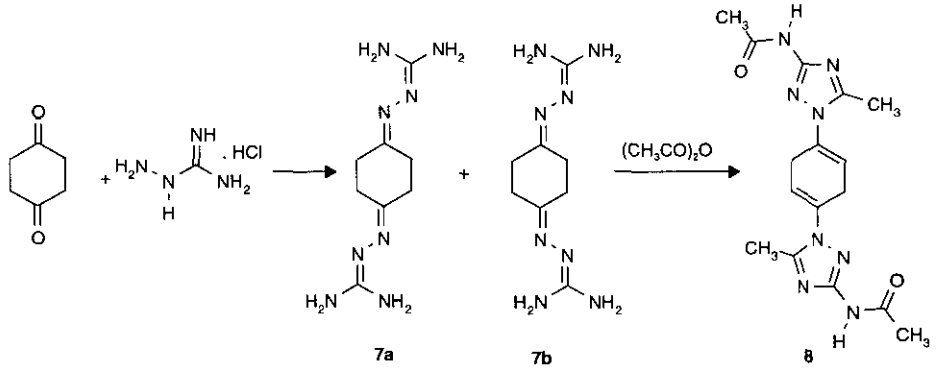
Scheme 1



Whereas with guanylhydrazones derived from cycloalkanones (**2a**), (**2b**), and (**2d**) the corresponding 3-acylamino-N^1-cycloalkenyl-5-methyl-1,2,4-triazoles (**3a**), (**3b**), and (**3d**) were obtained exclusively, with the cyclododecanone derivative (**2c**), besides the mono-*N*-acetyltriazole (**3c**) also the corresponding

N,N-diacetyl product (**4c**) was isolated from the reaction mixture by means of column chromatography. In the case of the guanylhydrazone derived from 4-chromanone, the hydrochloride salt (**2e•HCl**) reacted with sodium acetate / acetic anhydride leading to the triazole derivative (**3e**), however, also *N,N'*-diacetylated educt (**5e**) was obtained. In contrast, no cyclisation reaction was found to occur with the bulky camphor guanylhydrazone (**2g**), in this case the corresponding *N,N'*-diacetyl compound (**5g**) was the exclusive reaction product. On the other hand, treatment of 2-adamantanone guanylhydrazone (**2f**) with acetic anhydride again led to the formation of a 3-amino-1,2,4-triazole system, however, not of type (**3**) but with the triazole N^1 now incorporated in an *O,N*-acetal substructure[9] (**6f**). An explanation for this reaction behaviour might be the fact that - a hypothetic - compound (**3f**) would contain a bridgehead double bond (*S*-number[10] = 6) and thus would be characterized by a high strain energy. NMR-investigations of the product obtained upon treatment of 1,4-cyclohexandione with aminoguanidine hydrochloride revealed the presence of a 3 : 1 mixture of two stereoisomers (**7a**) and (**7b**) (Scheme 2). Successive reaction with acetic anhydride led to a high melting, low soluble product, to which we assign structure (**8**) according to micro-analysis, MS, ^{1}H-, and ^{13}C-NMR data.

Scheme 2



The reaction mechanism for the transformation of guanylhydrazones (**2**) (or (**7**)) into the corresponding 3-acetylamino-5-methyl-1,2,4-triazole derivatives (**3**) (or (**8**)) by action of acetic anhydride can be assumed similar to that given for the cyclisation of bisalkylideneaminooxamidines[11] (here a detailed step by step reaction mechanism is presented) or S-alkylisothiosemicarbazones[12] involving a 5-*endo-trig* ring closure[13,14] of an intermediate *N*-acetylguanylhydrazone.

NMR Spectroscopic Investigations

The NMR data of compounds (**2**) - (**8**) are given in the Experimental. Assignment of signals in the ^{1}H and ^{13}C-NMR spectra was achieved by a combination of different NMR techniques such as fully ^{1}H-coupled

^{13}C-NMR, APT,[15] NOE-difference spectroscopy,[16] 1D-TOCSY,[17] ^{13}C,^{1}H shift correlations *via* one bond couplings (HMQC)[18] and more than one bond couplings (HMBC),[19] 1D-HETCOR[20] and long-range INEPT[21] experiments with selective excitation.

Guanylhydrazones (**2**) can exist in two tautomeric forms (forms A and B, Scheme 1). ^{1}H-NMR investigations according to ref.[7] gave a strong hint that in DMSO-d_6 solution they exist in the diaminomethylene form (form A). Consideration of γ-effects enabled us to discriminate between *syn* and *anti* carbon atoms of the $C_{syn}C(=N-)C_{anti}$ partial structure in guanylhydrazones (**2a-c,f**) and (**7**): carbon atoms being in γ-position (α to C=N) to a *syn* located hydrazono N^2 atom suffer an upfield shift compared to the γ-atoms in *anti*-position due to steric compression.[22,23] Thus, for instance, with **2b** carbon atom C-2 (δ 26.8 ppm) was assigned to be '*syn*' and C-6 (δ 35.4 ppm) to be '*anti*' regarding the C^1=N-N^2 substructure. Based on similar ^{13}C-chemical shift considerations and on comparison with literature data of closely related compounds with known stereochemistry (*E*)-configuration can be assigned to the camphor derivatives (**2g**) and (**5g**) as well as to 1-indanone guanylhydrazone (**2d**) (high degree of correspondence in the ^{13}C chemical shifts and also ^{1}H-chemical shifts with (*E*)-camphor oxime[22,24] and (*E*)-1-indanone oxime derivatives,[25] respectively). (*E*)-Configuration of **2e•HCl** followed from an NOE-difference experiment as irradiation of the (sharp) N-H resonance with δ 11.46 ppm led to a strong enhancement of the signal due to chromanone H-3 thus clearly indicating spatial closeness of aminoguanidine side chain and cycloaliphatic protons. Discrimination of isomers (**7a**) and (**7b**) was easily possible considering the splitting patterns in the ^{1}H-NMR spectra. Whereas in **7a** the adjacent protons H-2 (δ 2.54 ppm) and H-3 (δ 2.36 ppm) (or H-5 and H-6, respectively) are not equivalent and thus give rise to two triplet signals (^3J = 6.9 Hz), in isomer (**7b**) adjacent protons (H-2, H-3) now are equivalent leading to two singlet signals of protons H-2, H-3 (δ 2.56 ppm) and H-5, H-6 (δ 2.35 ppm).

Apart from signals due to the N^1-substituent the NMR spectra of 1,2,4-triazole derivatives (**3a-f**) and (**8**) exhibit a high degree of similarity. In the ^{13}C-NMR spectra, the signals of triazole C-3 and triazole C-5 can be easily distinguished *via* their coupling patterns: in the gated decoupled spectra the signal of C-5 shows a characteristic quartet structure (^2J = 7.1 - 7.5 Hz) due to coupling with the methyl protons. In general, the shifts of triazole C-3 (δ 153.5 - 155.0 ppm) are somewhat larger than those of corresponding triazole C-5 nuclei (δ 150.6 - 152.9 ppm). Moreover, the ^{13}C-chemical shifts due to the *N*-acetyl system are located in a narrow range (CO: δ 167.5 - 168.0 ppm; COMe: δ 23.1 - 23.3 ppm). The resonance of the methyl protons attached to triazole C-5 (δ 2.33 - 2.53 ppm) was used as an irradiation target in NOE-difference experiments for the identification of signals due to the N^1-substituent. Thus, for instance, with **3d** the signals of indane H-2 and H-7 and with **3e** those of chromane H-3 and H-5 could be identified unambiguously in this way.

EXPERIMENTAL

Melting points were detected on a Boetius hot-stage microscope and are uncorrected. Solvents were distilled prior to use. MS spectra were obtained on a Shimadzu QP 1000 spectrometer (EI, 70 eV). All NMR spectra were recorded on a Varian Unity*plus* 300 spectrometer (299.95 MHz for ^{1}H, 75.43 MHz for ^{13}C) at 28°C. The solvent signal was used as an internal standard which was related to TMS with δ 2.49 ppm (^{1}H, DMSO-d_6) and δ 39.5 ppm (^{13}C, DMSO-d_6). The digital resolutions were 0.25 Hz/data point for the ^{1}H-NMR spectra, 0.56 Hz/data point for the broad-band decoupled ^{13}C-NMR spectra and 0.33 Hz/data point for the gated decoupled ^{13}C-NMR spectra.

2-Cyclopentylidene-1-hydrazinecarboximidamide (**2a**)

Aminoguanidine hydrogencarbonate (6.81 g, 50 mmol) was dissolved in 25 mL of 2N hydrochloric acid. After the evolution of carbon dioxide had ceased, 4.21 g (50 mmol) of cylopentanone was added and the reaction mixture was stirred for 2 h. The resulting clear solution was treated with excessive 2N KOH to precipitate the free base. Recrystallisation from ethanol afforded 5.33 g (76%) of colorless crystals, mp 161-163°C (lit.,[26] mp 158-159°C); ^{1}H-NMR (DMSO-d_6): δ (ppm) 1.62 (m, 4H, H-3,4), 2.22 (m, 4H, H-2,6), 5.33 (s, broad, 4H, NH_2); ^{13}C-NMR (DMSO-d_6): δ (ppm) 24.52 (C-3), 24.55 (C-4), 28.6 (C-2, *syn* to C^{1}=N-**N**), 32.4 (C-5, *anti* to C^{1}=N-**N**), 157.9 (N-C=N), 162.0 (C-1).

2-Cyclohexylidene-1-hydrazinecarboximidamide (**2b**)

Compound (**2b**) was prepared from equimolar amounts of aminoguanidine hydrogencarbonate and cyclohexanone similar to the procedure given for the preparation of **2a**. The hydrochloride salt (**2b·HCl**) precipitated after 5 min of stirring (yield: 72%, colorless crystals of mp 204-205°C), successive treatment with aqueous 2N KOH afforded 62% of **2b** (mp 53-54.5°C); ^{1}H-NMR (DMSO-d_6): δ (ppm) 1.47 (m, 2H, H-3), 1.54 (m, 4H, H-4, H-5), 2.14 (m, 2H, H-6, *anti* to C^{1}=N-**N**), 2.49 (m, 2H, H-2, *syn* to C^{1}=N-**N**), 5.11 (br s, 2H, NH_2), 5.44 (br s, 2H, NH_2); ^{13}C-NMR (DMSO-d_6): δ (ppm) 25.97 (C-4), 25.99 (C-3), 26.8 (C-2, *syn* to C^{1}=N-**N**), 27.3 (C-5), 35.4 (C-6, *anti* to C^{1}=N-**N**), 155.5 (C-1), 158.3 (N-C=N).

2-Cyclododecylidene-1-hydrazinecarboximidamide (**2c**)[27,28]

Aminoguanidine hydrogencarbonate (2.72 g, 20 mmol) was dissolved in 10 mL of 2N hydrochloric acid. After the evolution of carbon dioxide had ceased, a solution of 3.65 g (20 mmol) of cyclododecanone in methanol (20 mL) was added and the mixture was heated to reflux for 1 h. After cooling, the separated crystals were collected, dissolved in hot water (200 mL) and treated with excessive aqueous 2N KOH. Recrystallisation from methanol - water afforded 4.24 g (89%) of colorless crystals, mp 138-139°C (lit.,[27]

mp 142°C); ^{1}H-NMR (DMSO-d_6): δ (ppm) 1.17-1.47 (m, 14H, H-4 - H-10), 1.47 (m, 2H, H-3), 1.62 (m, 2H, H-11), 2.17 (m, 2H, H-12, *anti* to C^1=N-**N**), 2.42 (m, 2H, H-2, *syn* to C^1=N-**N**), 5.06 (br s, 2H, NH_2), 5.45 (br s, 2H, NH_2); ^{13}C-NMR (DMSO-d_6): δ (ppm) 22.2, 22.8 (C-9), 22.9, 23.0 (C-11), 23.2 (C-3), 23.8 (C-10), 24.4 (C-4), 24.9, 25.2, 27.5 (C-2, *syn* to C^1=N-**N**), 31.0 (C-12, *anti* to C^1=N-**N**), 154.8 (C-1), 158.2 (N-C=N).

(*E*)-2-(2,3-Dihydro-1*H*-1-indenylidene)-1-hydrazinecarboximidamide (**2d**)[28]

Aminoguanidine hydrogencarbonate (2.72 g, 20 mmol) was dissolved in 10 mL of 2N hydrochloric acid. After the evolution of carbon dioxide had ceased, a solution of 2.64 g (20 mmol) of 1-indanone (**1d**) in methanol (12 mL) was added and the mixture was heated to reflux for 1 h. Then the clear mixture was concentrated *in vacuo* and the precipitated salt was recrystallized from hot water to give 4.03 g (89%) of **2d·HCl**. Conversion to the free base by treatment with excessive aqueous 2N KOH afforded 3.05 g (81% regarding **1d**) of colorless crystals, mp 208-209°C; ^{1}H-NMR (DMSO-d_6): δ (ppm) 2.75 (m, 2H, H-2), 2.94 (m, 2H, H-3), 5.55 (br s, 2H, NH_2), 5.81 (br s, 2H, NH_2), 7.18 (m, 1H, H-6), 7.19 (m, 1H, H-5), 7.26 (m, 1H, H-4), 7.67 (m, 1H, H-7); ^{13}C-NMR (DMSO-d_6): δ (ppm) 27.6 (C-2), 28.0 (C-3), 120.4 (C-7), 125.3 (C-4), 126.3 (C-6), 128.2 (C-5), 140.0 (C-7a), 147.4 (C-3a), 156.9 (C-1), 159.4 (N-C=N).

(*E*)-2-(3,4-Dihydro-2*H*-4-chromenylidene)-1-hydrazinecarboximidamide Hydrochloride(**2e·HCl**)

Reaction of 4-chromanone and aminoguanidine hydrogencarbonate (similar as described for the preparation of **2c**) afforded 97% of **2e·HCl** as colorless crystals of mp 256-262°C; MS: m/z (%) 204 (M^+-HCl, 20), 176 (25), 161 (22), 120 (16), 119 (100), 103 (12), 91 (80), 78 (14), 77 (28), 65 (22), 64 (12), 63 (19), 58 (25), 57 (13), 55 (10), 52 (11), 51 (24); ^{1}H-NMR (DMSO-d_6): δ (ppm) 2.91 (t, J = 6.2 Hz, 2H, H-3), 4.26 (t, J = 6.2 Hz, 2H, H-2), 6.89 (dd, J = 8.2 Hz and 1.2 Hz, 1H, H-8), 6.96 (m, 1H, H-6), 7.30 (m, 1H, H-7), 7.89 (br s, 4H, NH_2), 8.28 (dd, J = 7.9 Hz and 1.7 Hz, 1H, H-5), 11.46 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6): δ (ppm) 26.2 (C-3), 64.3 (C-2), 117.3 (C-8), 119.5 (C-4a), 121.0 (C-6), 125.7 (C-5), 131.5 (C-7), 145.8 (C-4), 156.0 (N-C=N), 156.9 (C-8a). *Anal.* Calcd for $C_{10}H_{13}N_4OCl$: C, 49.90; H, 5.44; N, 23.28. Found: C, 50.12; H, 5.56; N, 23.14.

2-Tricyclo[3.3.1.1^{3,7}]dec-2-ylidene-1-hydrazinecarboximidamide (**2f**)[11]

Reaction of 2-adamantanone and aminoguanidine hydrogencarbonate (similar as described for the preparation of **2c**, however, reaction time 4 h) afforded 85% of **2f** as colorless crystals of mp 217-218°C; ^{1}H-NMR (DMSO-d_6): δ (ppm) 1.61 (m, 2H, H-8$_{ax}$,H-9$_{ax}$), 1.72 (m, 2H, H-4$_{ax}$,H-10$_{ax}$), 1.80 (m, 4H, H-6$_{eq}$,H-6$_{ax}$, H8$_{eq}$,H-9$_{eq}$), 1.89 (m, 2H, H-4$_{eq}$,H-10$_{eq}$), 1.91 (m, 2H, H-5,H-7), 2.41 (m, 1H, H-3, *anti* to C^2=N-**N**), 3.67 (m, 1H, H-1, *syn* to C^2=N-**N**), 5.07 (br s, 2H, NH_2), 5.46 (br s, 2H, NH_2); ^{13}C-NMR

(DMSO-d_6): δ (ppm) 27.7 (C-5,C-7), 30.5 (C-1, *syn* to C^2=N-**N**), 36.4 (C-6), 37.3 (C-8,C-9), 38.8 (C-4,C-10), 39.0 (C-3, *anti* to C^2=N-**N**), 158.3 (N-C=N), 162.1 (C-2).

(*E*)-2-(1,7,7-Trimethylbicyclo[2.2.1]hept-2-ylidene)-1-hydrazinecarboximidamide (**2g**)[30]

Reaction of rac. camphor and aminoguanidine hydrogencarbonate (similar as described for the preparation of **2c**, however, reaction time 6 h) and subsequent recrystallisation from ethanol - water afforded 57% of **2g** as colorless crystals of mp 211-213°C (lit.,[30] mp 219-221°C); ^{1}H-NMR (DMSO-d_6): δ (ppm) 0.67 (s, 3H, C7-Me, *cis* to side-chain), 0.86 (s, 3H, C7-Me, *trans* to side-chain), 0.91 (s, 3H, C1-Me), 1.11 (m, 1H, H-5_{endo}), 1.26 (m, 1H, H-6_{endo}), 1.63 (m, 1H, H-6_{exo}), 1.76 (m, 1H, H-5_{exo}), 1.80 (m, 1H, H-4), 1.85 (m, 1H, H-3_{endo}), 2.33 (m, 1H, H-3_{exo}), 5.15 (br s, 2H, NH_2), 5.39 (br s, 2H, NH_2); ^{13}C-NMR (DMSO-d_6): δ (ppm) 11.7 (C1-*Me*), 18.7 (C7-*Me*, *trans* to side-chain), 19.3 (C7-*Me*, *cis* to side-chain), 27.1 (C-5), 32.9 (C-6), 35.3 (C-3), 43.5 (C-4), 47.0 (C-7), 51.0 (C-1), 158.1 (N-C=N), 164.6 (C-2).

2,2'-(1,4-Cyclohexanediylene)-bis-1-hydrazinecarboximidamide (**7**)[31]

Reaction of 1,4-cyclohexanedione and aminoguanidine hydrogencarbonate (similar as described for the preparation of **2b**) afforded, after crystallisation from water, 84% of the dihydrochloride salt (**7**•2**HCl**) as colorless crystals of mp 265°C (lit.,[32] mp 250-251°C). The free base was recrystallized from water to give 69% of yellowish crystals of mp 230-232°C (lit.,[31] mp 230°C). NMR analysis revealed this product to be a 3 : 1 mixture of stereoisomers **7a** and **7b**. Compound (**7a**) (*E*,*E*-isomer): ^{1}H-NMR (DMSO-d_6): δ (ppm) 2.36 (t, ^3J = 6.9 Hz, 4H, H-3,6, *anti* to C=N-**N**), 2.54 (t, ^3J = 6.9 Hz, 4H, H-2,5, *syn* to C=N-**N**) , 5.07 (b s, 4H, NH_2), 5.48 (br s, 4H, NH_2); ^{13}C-NMR (DMSO-d_6): δ (ppm) 26.8 (C-2,5, *syn* to C=N-**N**), 31.3 (C-3,6, *anti* to C=N-**N**), 154.4 (C-1,4), 158.2 (N-C=N). Compound (**7b**) (*Z*,*Z*-isomer): ^{1}H-NMR (DMSO-d_6): δ (ppm) 2.35 (s, 4H, H-5,6, *anti* to C=N-**N**), 2.56 (s, 4H, H-2,3, *syn* to C=N-**N**), 5.07 (br s, 4H, NH_2), 5.48 (br s, 4H, NH_2); ^{13}C-NMR (DMSO-d_6): δ (ppm) 24.7 (C-2,3, *syn* to C=N-**N**), 33.7 (C-5,6, *anti* to C=N-**N**), 154.3 (C-1,4), 158.3 (N-C=N).

General Procedure for the Reaction of Hydrazinecarboximidamides with Acetic Anhydride

A suspension of 5 mmol of the hydrazinecarboximidamide (**2a-d**, **f**, **g**) or (**7**), respectively, in acetic anhydride (7 mL, 74 mmol) was stirred at 100°C (bath temperature) for 1 h. Then the reaction mixture was evaporated *in vacuo* and the semicrystalline residue was 2-3 times co-distilled with toluene (20 mL each) to remove volatile components. Finally, the residue was recrystallized from the appropriate solvent.

*N*1-[1-(1-Cyclopentenyl)-5-methyl-1*H*-1,2,4-triazol-3-yl]acetamide (**3a**)

Yield: 46% of colorless crystals, mp 173-175°C (ethanol); MS: m/z (%) 206 (M^+, 24), 165 (11), 164 (100), 163 (16), 137 (12), 123 (42), 122 (41), 98 (43), 95 (16), 94 (14), 82 (12), 81 (40), 80 (25), 69 (18),

68 (11), 67 (33), 66 (13), 65 (22), 57 (14), 56 (16), 55 (21), 54 (57), 53 (29), 52 (12); ^{1}H-NMR (DMSO-d_6): δ (ppm) 1.96 (m, 2H, cyclo H-4), 2.01 (s, 3H, COMe), 2.44 (s, 3H, triazole C5-Me), 2.49 (m, 2H, cyclo H-3), 2.75 (m, 2H, cyclo H-5), 5.84 (m, 1H, cyclo H-2), 10.22 (br s, 1H, NH); ^{13}C-NMR (DMSO-d_6): δ (ppm) 13.4 (triazole C5-*Me*, ^1J = 130.0 Hz), 21.3 (cyclo C-4), 23.1 (CO*Me*, ^1J = 128.3 Hz), 30.6 (cyclo C-3), 32.6 (cyclo C-5), 118.9 (cyclo C-2), 137.7 (cyclo C-1), 151.4 (triazole C-5, $^2J_{C\text{-}5,C5\text{-}Me}$ = 7.1 Hz), 154.7 (triazole C-3), 168.0 (C=O). *Anal.* Calcd for $C_{10}H_{14}N_4O$: C, 58.24; H, 6.84; N, 27.16. Found: C, 58.48; H, 6.77; N, 27.22.

*N*1-[1-(1-Cyclohexenyl)-5-methyl-1*H*-1,2,4-triazol-3-yl]acetamide (**3b**)

Yield: 60% of colorless crystals, mp 142-143°C (ethanol); MS: m/z (%) 220 (M^+, 8), 178 (40), 140 (29), 99 (12), 98 (100), 95 (11), 67 (16), 57 (31), 56 (20), 55 (29), 54 (20), 53 (13); ^{1}H-NMR (DMSO-d_6): δ (ppm) 1.60 (m, 2H, cyclo H-4), 1.72 (m, 2H, cyco H-5), 2.00 (s, 3H, COMe), 2.33 (s, 3H, triazole C5-Me), 2.17 (m, 2H, cyclo H-3), 2.29 (m, 2H, cyclo H-6), 5.88 (m, 1H, cyclo H-2), 10.18 (br s, 1H, NH); ^{13}C-NMR (DMSO-d_6): δ (ppm) 12.5 (triazole C5-*Me*, ^1J = 128.9 Hz), 21.0 (cyclo C-4), 21.9 (cyclo C-5), 23.1 (CO*Me*, ^1J = 128.1 Hz), 23.8 (cyclo C-3), 27.2 (cyclo C-6), 123.8 (cyclo C-2, ^1J = 158.2 Hz), 134.5 (cyclo C-1), 150.6 (triazole C-5, $^2J_{C\text{-}5,C5\text{-}Me}$ = 7.1 Hz), 154.7 (triazole C-3), 167.8 (C=O). HRMS: Calcd for $C_{11}H_{16}N_4O$: 220.13241. Found: 220.1324 ± 0.001.

*N*1-[1-(1-Cyclododecenyl)-5-methyl-1*H*-1,2,4-triazol-3-yl]acetamide (**3c**) and *N*1-Acetyl-*N*1-[1-(1-cyclododecenyl)-5-methyl-1*H*-1,2,4-triazol-3-yl]acetamide (**4c**)

The crude product was subjected to column chromatography (eluent: toluene - ethanol, 7 : 3) to afford 15% of **4c** (faster eluted component) and 45% of **3c** (slower eluted component). Compound **3c**: colorless crystals of mp 136-137°C; MS: m/z (%) 304 (M^+, 2), 205 (16), 193 (12), 179 (40), 166 (13), 163 (13), 149 (19), 141 (100), 137 (26), 123 (13), 121 (12), 99 (30), 98 (29), 96 (14), 95 (17), 94 (13), 93 (13), 85 (11), 83 (25), 82 (19), 81 (43), 80 (25), 79 (25), 77 (12), 70 (11), 69 (62), 68 (26), 67 (59), 65 (11), 57 (26), 56 (19), 55 (92), 54 (41), 53 (34); ^{1}H-NMR (DMSO-d_6): δ (ppm) 1.17 (m, 2H, cyclo H-11), 1.34 (m, 12H, cyclo H-5 - H-10), 1.52 (m, 2H, cyco H-4), 2.00 (s, 3H, COMe), 2.34 (s, 3H, triazole C5-Me), 2.23 (m, 2H, cyclo H-3), 2.54 (m, 2H, cyclo H-12), 5.58 (t, J = 8.1 Hz, 2H, cyclo H-2), 10.16 (br s, 1H, NH); ^{13}C-NMR (DMSO-d_6): δ (ppm) 12.4 (triazole C5-*Me*, ^1J = 129.7 Hz), 21.4, 21.8, 23.1 (CO*Me*, ^1J = 128.1 Hz), 23.3 (cyclo C-11), 23.4, 23.9 (cyclo C-3), 24.1 (cyclo C-5), 24.3, 25.3 (cyclo C-12), 26.0 (cyclo C-4), 128.9 (cyclo C-2), 135.7 (cyclo C-1), 151.3 (triazole C-5), 154.8 (triazole C-3), 167.8 (C=O). *Anal.* Calcd for $C_{17}H_{28}N_4O$: C, 67.07; H, 9.27; N, 18.40. Found: C, 67.33; H, 9.21; N, 18.19. Compound **4c**: colorless crystals of mp 127-128°C; MS: m/z (%) 346 (M^+, 1), 289 (36), 205 (16), 179 (45), 163 (11), 141 (100), 140 (12), 137 (18), 125 (67), 123 (14), 99 (21), 98 (13), 95 (13), 94 (11), 83 (13), 82 (17), 81

(24), 80 (22), 79 (23), 77 (11), 69 (21), 68 (17), 67 (55), 65 (10), 56 (13), 55 (83), 54 (35), 53 (30); ^{1}H-NMR (DMSO-d_6): δ (ppm) 1.15 - 1.50 (m, 14H, cyclo H-5 - H-11), 1.53 (m, 2H, cyclo H-4), 2.19 (s, 6H, COMe), 2.27 (m, 2H, cyclo H-3), 2.45 (s, 3H, triazole C5-Me), 2.57 (m, 2H, cyclo H-12), 5.73 (t, J = 8.1 Hz, 1H, cyclo H-2); ^{13}C-NMR (DMSO-d_6): δ (ppm) 12.6 (triazole C5-*Me*), 21.5, 21.7, 23.1, 23.6, 23.9 (cyclo C-3), 24.0, 24.1, 25.3 (CO*Me*), 25.9 (cyclo C-4), 130.0 (cyclo C-2), 135.5 (cyclo C-1), 153.7 (triazole C-5), 154.7 (triazole C-3), 171.5 (C=O). *Anal.* Calcd for $C_{19}H_{30}N_4O_2$: C, 65.87; H, 8.73; N, 16.17. Found: C, 66.05; H, 8.87; N, 16.25.

*N*1-[1-(1*H*-3-Indenyl)-5-methyl-1*H*-1,2,4-triazol-3-yl]acetamide (**3d**)

Yield: 52% of colorless crystals, mp 162-165°C (toluene); MS: m/z (%) 254 (M^+, 7), 220 (10), 178 (47), 164 (26), 149 (13), 140 (17), 137 (14), 129 (28), 123 (13), 122 (12), 115 (19), 99 (15), 98 (100), 97 (15), 96 (17), 95 (23), 94 (12), 91 (12), 85 (13), 84 (11), 83 (21), 82 (14), 81 (32), 80 (17), 79 (18), 77 (17), 73 (32), 71 (24), 70 (16), 69 (45), 68 (23), 67 (41), 66 (12), 65 (16), 63 (12), 60 (39), 57 (74), 56 (46), 55 (95), 54 (47), 53 (31), 52 (13), 51 (17), 45 (42); ^{1}H-NMR (DMSO-d_6): δ (ppm) 2.09 (br s, 3H, COMe), 2.48 (s, 3H, triazole C5-Me), 3.64 (d, J = 2.2 Hz, 2H, ind H-3), 6.78 (t, J = 2.2 Hz, 1H, ind H-2), 7.32 (m, 2H, ind H-5, ind H-6), 7.55 (m, 1H, ind H-4), 7.61 (m, 1H, ind H-7), 10.41 (br s, 1H, NH); ^{13}C-NMR (DMSO-d_6): δ (ppm) 12.6 (triazole C5-*Me*, ^1J = 130.1 Hz), 23.3 (CO*Me*, ^1J = 128.3 Hz), 36.3 (ind C-3, ^1J = 130.7 Hz), 120.6 (ind C-7), 124.2 (ind C-4), 125.9 (ind C-5), 126.2 (ind C-2), 126.3 (ind C-6), 137.3 (ind C-1), 139.3 (ind C-7a), 142.7 (ind C-3a), 152.5 (triazole C-5, $^2J_{C\text{-}5,C5\text{-}Me}$ = 7.3 Hz), 155.5 (triazole C-3), 167.8 (C=O). *Anal.* Calcd for $C_{14}H_{14}N_4O$: C, 66.13; H, 5.55; N, 22.03. Found: C, 66.13; H, 5.55; N, 21.88.

*N*1-[1-(2*H*-4-Chromenyl)-5-methyl-1*H*-1,2,4-triazol-3-yl]acetamide (**3e**) and *N*1-[(Acetylamino)-2-(3,4-dihydro-2*H*-4-chromenylidene)carbohydrazonoyl]acetamide (**5e**)

A mixture of compound **2e·HCl** (2.41 g, 10 mmol), sodium acetate (0.82 g, 10 mmol) and acetic anhydride (7 mL, 74 mmol) was stirred at 100°C for 1.5 h. Then the reaction mixture was poured onto ice - water, the separated crystals were filtered off, washed with water and dried to afford 0.48 g (17%) of **5e** (recrystallisation from ethanol - water gave colorless crystals of mp 167-172°C). The aqueous filtrate was repeatedly extracted with chloroform, the combined organic phases were washed with water, dried ($MgSO_4$) and evaporated *in vacuo*. The solid residue was recrystallized from ethanol - hexane to give 53% of **3e** as colorless crystals of mp 147-148°C. Compound (**3e**): MS: m/z (%) 270 (M^+, 19), 228 (24), 227 (24), 186 (16), 178 (21), 164 (17), 145 (14), 144 (17), 140 (13), 131 (19), 130 (10), 129 (12), 119 (11), 102 (15), 98 (100), 95 (13), 91 (17), 83 (11), 81 (22), 77 (25), 73 (18), 71 (13), 69 (39), 68 (13), 67 (24), 65 (11), 64 (12), 63 (14), 60 (22), 57 (48), 56 (46), 55 (50), 54 (24), 53 (18), 51 (20), 50 (10), 45 (24);

^{1}H-NMR (DMSO-d_6): δ (ppm) 2.04 (br s, 3H, COMe), 2.33 (s, 3H, triazole C5-Me), 5.00 (d, J = 3.8 Hz, 2H, chrom H-2), 6.22 (t, J = 3.8 Hz, 1H, chrom H-3), 6.62 (m, 1H, chrom H-5), 6.87 (m, 1H, chrom H-6), 6.88 (m, 1H, chrom H-8), 7.21 (m, 1H, chrom H-7), 10.36 (br s, 1H, NH); ^{13}C-NMR (DMSO-d_6): δ (ppm) 11.8 (triazole C5-*Me*, ^1J = 130.1 Hz), 23.2 (CO*Me*, ^1J = 128.1 Hz), 64.7 (chrom C-2, ^1J = 150.1 Hz, ^2J = 7.9 Hz), 115.9 (chrom C-8), 119.6 (chrom C-4a), 121.4 (chrom C-6), 121.6 (chrom C-3, ^1J = 168.5 Hz, ^2J = 5.2 Hz), 123.2 (chrom C-5), 130.5 (chrom C-7), 130.7 (chrom C-4), 152.8 (triazole C-5, ^2J = 7.5 Hz), 154.1 (chrom C-8a), 155.8 (triazole C-3), 167.5 (C=O). *Anal.* Calcd for $C_{14}H_{14}N_4O_2$: C, 62.21; H, 5.22; N, 20.73. Found: C, 61.98; H, 5.38; N, 21.00. Compound (**5e**): MS: m/z (%) 288 (M^+, 15), 264 (17), 263 (17), 218 (39), 176 (52), 172 (74), 161 (31), 146 (55), 131 (60), 119 (33), 98 (43), 91 (43), 69 (100), 64 (60), 55 (72), 54 (46), 45 (25); ^{1}H-NMR (DMSO-d_6): δ (ppm) 2.13 (s, 3H, COMe), 2.19 (s, 3H, COMe), 2.99 (t, J = 6.2 Hz, 2H, chrom H-3), 4.24 (t, J = 6.2 Hz, 2H, chrom H-2), 6.90 (m, 1H, chrom H-8), 6.98 (m, 1H, chrom H-6), 7.32 (m, 1H, chrom H-7), 8.25 (m, 1H, chrom H-5), 9.86 (s, 1H, NH), 10.43 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6): δ (ppm) 24.0 (CO*Me*, ^1J = 128.9 Hz), 24.8 (CO*Me*, ^1J = 129.0 Hz), 26.4 (chrom C-3, ^1J = 131.1 Hz), 65.2 (chrom C-2, ^1J = 148.2 Hz), 117.2 (chrom C-8), 120.5 (chrom C-4a), 120.8 (chrom C-6), 125.4 (chrom C-5), 131.6 (chrom C-7), 144.2 (N-C=N), 154.9 (chrom C-4), 157.4 (chrom C-8a), 169.6 (C=O, connected with Me 24.8/2.19 ppm), 170.1 (C=O, connected with Me 24.0/2.13 ppm). *Anal.* Calcd for $C_{14}H_{16}N_4O_3$: C, 58.32; H, 5.59; N, 19.43. Found: C, 58.57; H, 5.62; N, 19.15.

2-[3-Acetylamino-5-methyl-1*H*-1,2,4-triazol-1-yl]-2-adamantyl Acetate (**6f**)

Yield: 10% of colorless crystals, mp 173-174°C (ethyl acetate - hexane); MS: m/z (%) 332 (M^+, < 1), 151 (29), 141 (12), 140 (43), 98 (100), 91 (13), 79 (21), 67 (13), 57 (20), 56 (31), 55 (15); ^{1}H-NMR (DMSO-d_6): δ (ppm) 1.66-1.88 (m, 10H, ada H), 1.95-2.08 (m, 2H ada H), 1.99 (br s, 3H, NCO*Me*), 2.01 (s, 3H, OCO*Me*), 2.53 (s, 3H, triazole C5-Me), 3.15 (m, 2H, ada H-1,3), 10.17 (br s, 1H, NH); ^{13}C-NMR (DMSO-d_6): δ (ppm) 15.3 (triazole C5-*Me*, ^1J = 130.1 Hz), 21.2 (OCO*Me*, ^1J = 129.8 Hz), 23.1 (NCO*Me*, ^1J = 128.0 Hz), 25.3, 25.8, 33.0, 33.2, 33.5 (ada C-1,3), 36.5 (ada C-6), 95.5 (ada C-2), 152.9 (triazole C-5), 153.5 (triazole C-3), 167.8 (NC=O), 168.4 (OC=O). HRMS: Calcd for $C_{17}H_{24}N_4O_3$: 332.18484. Found: 332.1848 ± 0.0015.

N1-[Acetylamino-2-(1,7,7-trimethylbicyclo[2.2.1]hept-2-ylidene)carbohydrazonoyl]acetamide (**5g**)

Yield: 87% of colorless crystals, mp 94-95°C (ethanol - water); MS: m/z (%) 292 (M^+, 12), 277 (19), 249 (22), 235 (29), 150 (53), 134 (46), 102 (58), 93 (63), 81 (40), 77 (60), 69 (49), 67 (69), 60 (64), 55 (100), 54 (43), 53 (51), 48 (50), 45 (41); ^{1}H-NMR (DMSO-d_6): δ (ppm) 0.72 (s, 3H, C7-Me, *cis* to side chain), 0.90 (s, 3H, C7-Me, *trans* to side chain), 1.00 (s, 3H, C1-Me), 1.18 (m, 1H, H-5_{endo}), 1.35 (m, 1H, H-6_{endo}), 1.69 (m, 1H, H-6_{exo}), 1.79 (m, 1H, H-5_{exo}), 1.87 (m, 1H, H-4), 1.97 (m, 1H, H-3_{endo}), 2.04 (s, 3H,

COMe), 2.11 (s, 3H, COMe), 2.46 (m, 1H, H-3_{exo}), 9.58 (br s, 1H, NH), 10.17 (br s, 1H, NH); ^{13}C-NMR (DMSO-d_6): δ (ppm) 11.2 (C1-*Me*), 18.5 (C7-Me, *trans* to side-chain), 19.3 (C7-*Me*, *cis* to side chain), 23.8 (CO*Me*), 24.5 (CO*Me*), 26.8 (C-5), 32.2 (C-6), 35.7 (C-3), 43.2 (C-4), 47.4 (C-7), 52.2 (C-1), 142.9 (N-C=N), 169.3 (C=O, connected with Me 23.8/2.04 ppm), 169.7 (C=O, connected with Me 24.5/2.11 ppm), 178.0 (C-2). *Anal.* Calcd for $C_{15}H_{24}N_4O_2$: C, 61.62; H, 8.27; N, 19.16. Found: C, 61.55; H, 8.54; N, 19.18.

*N*1-(1-{4-[3-Acetylamino-5-methyl-1*H*-1,2,4-triazol-1-yl]-1,4-cyclohexadienyl]-5-methyl-1*H*-1,2,4-triazol-3-yl}acetamide (**8**)

Yield: 34% of colorless crystals, mp 333-334°C; MS: m/z (%) 356 (M^+, 34), 355 (100), 337 (26), 313 (36), 189 (23), 174 (41), 148 (15), 147 (12), 134 (16), 133 (30), 106 (13), 105 (16), 92 (27), 91 (40), 79 (20), 78 (23), 77 (35), 67 (14), 66 (20), 65 (49), 64 (19), 63 (12), 56 (23), 54 (18), 53 (19), 52 (30), 51 (32); ^{1}H-NMR (DMSO-d_6): δ (ppm) 2.03 (br s, 6H, COMe), 2.47 (s, 6H, triazole C5-Me), 2.85 (s, 4H, cyclo H-3,6), 6.26 (s, 2H, cyclo H-2,5), 10.31 (br s, 2H, NH); ^{13}C-NMR (DMSO-d_6): δ (ppm) 13.4 (triazole C5-*Me*), 23.2 (CO*Me*), 25.6 (cyclo C-3,6), 115.5 (cyclo C-2,5), 133.0 (cyclo C-1,4), 151.7 (triazole C-5), 155.0 (triazole C-3), 167.9 (C=O). *Anal.* Calcd for $C_{16}H_{20}N_8O_2$: C, 53.92; H, 5.66; N, 31.44. Found: C, 54.00; H, 5.84; N, 31.14.

REFERENCES AND NOTES

1. J. Thiele, *Ann. Chem.*, 1892, **270**, 1.
2. P. H. Richter, I. Wunderlich, M. Schleuder, and A. Keckeis, *Pharmazie*, 1993, **48**, 83.
3. P. H. Richter, I. Wunderlich, M. Schleuder, and A. Keckeis, *Pharmazie*, 1993, **48**, 163.
4. F. Kurzer and L. E. A. Godfrey, *Angew. Chem.*, 1963, **75**, 1157.
5. Z. Györgydeák, W. Holzer, R. W. Kunz, and A. Linden, *Monatsh. Chem.*, 1995, **126**, 733.
6. Z. Györgydeák, W. Holzer, and J. Thiem, *Carbohydr. Res.*, 1997, **302**, 229.
7. W. Holzer and Z. Györgydeák, *Monatsh. Chem.*, 1992, **123**, 1163.
8. W. Holzer and Z. Györgydeák, *J. Heterocycl. Chem.*, 1996, **33**, 675.
9. It should be mentioned that formation of a similar *O,N*-acetal compound was observed upon reaction of pyridine-4-carbaldehyde guanylhydrazone with acetic anhydride (ref.[5]).
10. F. S. Fawcett, *Chem. Rev.*, 1950, **47**, 219.
11. M. J. Cooper, R. Hull, and M. Wardleworth, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1433.
12. E. B. Usova, G. D. Krapivin, V. E. Zavodnik, and V. G. Kul'nevich, *Khim. Geterotsikl. Soedin.*, 1990, 931 (*Chem. Abstr.*, 1991, **115**, 49516e).

13. J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 1976, 734.
14. C. D. Johnson, *Acc. Chem. Res.*, 1993, **26**, 476.
15. S. L. Patt and J. N. Shoolery, *J. Magn. Reson.*, 1982, **46**, 535.
16. D. Neuhaus and M. P. Williamson, *'The Nuclear Overhauser Effect in Structural and Conformational Analysis'*, VCH Publishers, New York, 1989.
17. D. G. Davis and A. Bax, *J. Am. Chem. Soc.*, 1985, **107**, 7197.
18. A. Bax and S. Subramanian, *J. Magn. Reson.*, 1986, **67**, 565.
19. A. Bax and M. F. Summers, *J. Am. Chem. Soc.*, 1986, **108**, 2093.
20. S. K. Sarkar and A. Bax, *J. Magn. Reson.*, 1985, **62**, 109.
21. A. Bax, *J. Magn. Reson.*, 1984, **57**, 314.
22. G. E. Hawkes, K. Herwig, and J. D. Roberts, *J. Org. Chem.*, 1974, **39**, 1017.
23. G. C. Levy and G. L. Nelson, *J. Am. Chem. Soc.*, 1972, **94**, 4897.
24. N. N. Majeed, G. S. MacDougall, and A. L. Porte, *J. Chem. Soc., Perkin Trans. 2*, 1988, 1027.
25. H. Irie, S. Tanaka, Y. Zhang, J. Koyama, T. Taga, and K. Machida, *Chem. Pharm. Bull.*, 1988, **36**, 3134.
26. I. Busko-Oszczapowicz, A. Lukasiewicz, W. Kotula, and J. Cieslak, *Acta Pol. Pharm.*, 1978, **35**, 181 (*Chem. Abstr.*, 1978, **89**, 215323f).
27. J. Nordmann, G. D. Mattioda, and G. P. M. H. Loiseau (Ugine Kuhlmann), Ger. Offen. 2,149,930 (20 Apr 1972) (*Chem. Abstr.*, 1972, **77**, 47951r).
28. R. M. Soll, P. J. Dollings, R. D. Mitchell, and D. A. Hafner, *Eur. J. Med. Chem.*, 1994, **29**, 223.
29. H. J. Panneman and A. H. N. M. Bruins (Akzo N. V.), Ger. Offen. 2,524,114 (18 Dec 1975) (*Chem. Abstr.*, 1976, **84**, 121830p).
30. R. N. Prasad and A. F. McKay, *Can. J. Chem.*, 1967, **45**, 2247.
31. T.-L. Chen, *Huaxue Xuebao*, 1958, **24**, 349 (*Chem. Abstr.*, 1959, **53**, 19921a).
32. S. Petersen, W. Gauss, and E. Urbschat, *Angew. Chem.*, 1955, **67**, 217.

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