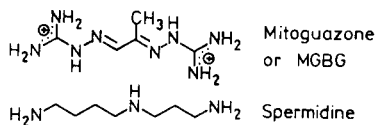


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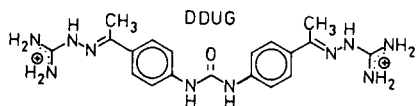
We have found previously that two 5-acetyl-4-methylpyrimidines could be transformed by aminoguanidine hydrochloride into 4-acetyl-1-amidino-3-methylpyrazolyl amidinohydrazone dihydrochloride. This reaction beside the fact that it led to a molecule closely related to the antitumor drug M.G.B.G. pointed out to a new possibility of ring contraction of pyrimidines into pyrazoles. We attempted therefore to study the possibility of extending this transformation to other substituted hydrazines and to define more accurately the conditions of this reaction as well as to prepare new potential anticancer drugs.

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Among anticancer drugs mitoguazone or methylglyoxal-bis(guanylhydrazone) (MGBG) [1] has the striking feature of being structurally related to spermidine [2], and is a good inhibitor of the enzyme *S*-adenosylmethioninedecarboxylase (SAM_D) [3].



In the present work we tried to synthesize new analogs of MGBG and diacetyldiphenylurea bis(guanylhydrazone) (DDUG) which have well established antitumor properties [1,3].



To do so, we hypothesized that replacement of the phenyl rings of DDUG by pyrimidine ones could be of pharmacological interest and we have thus been led at first to do a systematic survey of the reaction of simple or substituted hydrazines like hydrazine, methylhydrazine, phenylhydrazine, aminoguanidine, semicarbazide and thiosemicarbazide on 5-acetyl-2-methylthio-4-methylpyrimidine **1**. This pyrimidine derives from condensation of *S*-methylisothiuronium with ethoxymethylene-acetylacetone (EMAA) **2** [4].

We observed that in hot acidic medium hydrazines **3a**, **3b**, **3c** and **3d** react with pyrimidine **1** and, by a ring contraction unexpected in the conditions of the experiment, give pyrazoles **4a**, **4b**, **4d** [5,6] and **4g** whereas the same reagents used at room temperature in a neutral or slightly acidic medium yield the corresponding hydrazones **5b**, **5d** and **5e**.

Hydrazine **3a** itself used in methanolic medium with the

starting material **1** gives at first, at room temperature, hydrazine **5a** then, upon boiling, the corresponding hydrazone **5b**. One owes probably the facile formation of 2-hydrazinopyrimidine **5a** to the electron attracting effect of the acetyl group in the 5-position which facilitates nucleophilic attack in position 2 of molecule **1**. This special reactivity in position 2 has been mentioned yet, mainly for 2-chloro-5-nitropyrimidine [7]. Acetylpyrazoles **4b** reacting with hydrazine hydrate give the corresponding azines **4c**.

By hot hydrolysis of **4d** one obtains, beside a small yield of **4f**, the corresponding amidinohydrazone **4e**, which emphasize the lability of amidino group of compound **4d**. As *N*-carbamoyl and *N*-thiocarbamoyl groups are much more unstable than the amidino one [8], as expected, compounds **4h** are the only products isolated from the reaction. The existence of pyrazoles **4g** are only postulated as unstable intermediates: These latter are also prepared by action of excess semicarbazide or thiosemicarbazine **3d** upon pyrazoles **4f**. As expected reaction of amidinohydrazone hydrochloride **3c** with acetylpyrazole **4f** gives back compound **4d**.

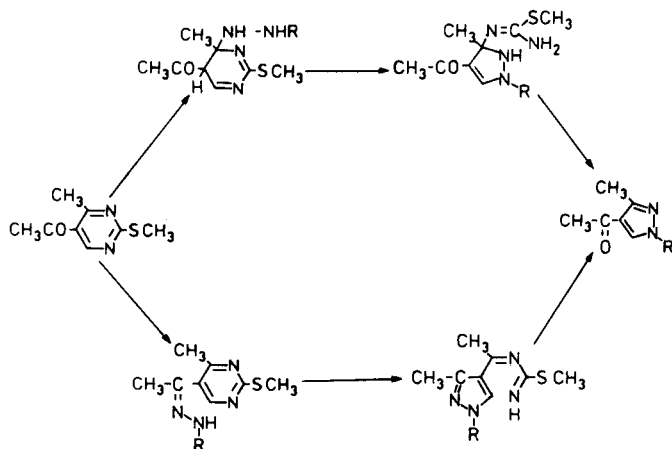
Beside this formation of pyrazoles, by ring contraction of pyrimidine **1** reacting with hydrazines **3**, and in order to have spectral evidences of the structures of these pyrazoles, we were led also to allow reaction of the same hydrazines **3** on EMAA **2**. These reactions carried in methanolic acidic medium at -15° gave, as expected [9], the corresponding pyrazoles. The structures of most of these pyrazoles are isomeric with those synthesized from **1**. So, starting with hydrazines **3a** and **3b**, one ends with acetylpyrazoles **6a** [10] that can be converted to the corresponding azines **6b** by action of hydrazine hydrate. Compound **6c** is obtained if the ratio of phenylhydrazine to compound **2** is increased.

According to the molecular proportion of the reagents hydrazine compounds **3c** or **3e** to compound **2**, and to the temperature of the reaction, either pyrazoles **6d** and **6e** are synthesized or their corresponding hydrazones **6f** and **6g**.

In fact, equimolar amounts of substituted hydrazines **3c** or **3d** and compound **2** lead, at low temperature, respectively through a simple condensation to **6d** and, (when $R = -CS-NH_2$) through a condensation followed by a hydrolysis of the thiocarbamoyl group, to **6e** (identical to **4f**). This later compound is also formed by alkaline cleavage of pyrazole **6d**. Furthermore, if two moles of reactants **3c** or **3d** are made to react with one mole of **2**, the compounds **6f** are synthesized that can lead to pyrazoles **6g** by alkaline cleavage or heating in boiling methanol.

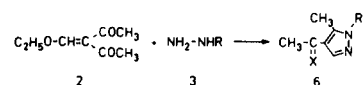
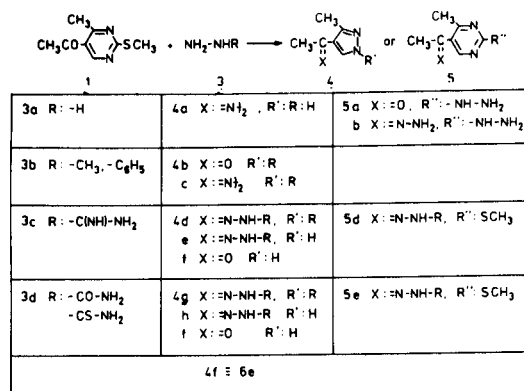
To our knowledge transformation of pyrimidines into pyrazoles in acidic medium has not been described yet. However the chemical literature quotes some examples of such ring contraction by action of hydrazine or methylhydrazine in basic medium [11] but in such conditions, with pyrimidine **1**, we only obtained single substitution in 2-position.

All our observations resulted in the fact that for every unsymmetrical substituted hydrazines we used we were able to make by choice, one type of pyrazolic position isomer from EMAA **2** and the other type, hitherto not mentioned in the literature, from pyrimidine **1**. This fact implies that in the case of compound **2** the carbon atom bearing the ethoxy group is attacked first by the primary amino group of the monosubstituted hydrazine, while pyrimidine **1** in acidic medium is not attacked by this primary amino group on carbon 6 (unsubstituted) but on carbon 4 (bearing a methyl group). Less likely if one bears in mind the nature of the reaction products obtained from methylhydrazine and phenylhydrazine, it could be imagined that pyrimidine **1** is attacked, in a first step, by the primary amine group at the carbonyl moiety and that a further attack of the hydrazonic $-NH-$ on carbon 6 of pyrimidine **1** leads to pyrazole formation.



In the present work we prepared by an univocal method an homogenous series of isomeric pyrazoles not previously known in the literature because they are not easily available by the classical methods [12] and so we have contri-

buted to an interesting systematic study. Moreover we possess now several original structures closely resembling those of spermidine and mitoguazone (mainly compounds **4d**, **6f**, etc...) and deserving study of their biological properties.



3a R: -H	6a X: =O, R': R
b R: -CH ₃ , -C ₆ H ₅	b X: =NH ₂ , R': R
	c X: =N-NH-C ₆ H ₅ , R': C ₆ H ₅
3c R: -CINHI-NH ₂	6d X: =O, R': R
d R: -CONH ₂ , -CSNH ₂	e X: =O, R': H
	f X: =N-NH-R, R': R
	g X: =N-NH-R, R': H
when R': H 6a ≡ 6e ≡ 4f	

EXPERIMENTAL

The ¹H nmr spectra were recorded on a Hitachi-Perkin Elmer 60 MHz spectrometer or a Varian 390 90 MHz spectrometer using dimethylsulfoxide-d₆ as the solvent and TMS as the internal reference. (Peak of water if present is not reported.) Chemical shifts are given in ppm. Melting points were taken on a Köfler bench and are uncorrected. Mass spectra were recorded, by electronic impact, with a Ribermag R10-10 apparatus using a direct inlet system. Elemental microanalyses were performed by Service Central d'Analyses (CNRS, P.B. 22, Vernaison, France).

The ¹³C nmr spectra of two compounds were recorded on a Bruker apparatus, using dimethylsulfoxide-d₆ as the solvent and tetramethylsilane as the internal reference.

Amidinohydrazine (or Aminoguanidine) Hydrochloride **3c**.

This compound was obtained in a cold aqueous solution by action of the requisite volume of concentrated hydrochloric acid on aminoguanidine hydrogenocarbonate dissolved in water.

4-Acetyl-3-methylpyrazole Azine **4a**.

From **1**.

Refluxing overnight a solution of pyrimidine **1** (0.45 g, 0.0025 mole), 1 ml (0.02 mole) of hydrazine hydrate in 50 ml of methanol acidified to pH = 1 with concentrated hydrochloric acid gave after cooling and partial solvent evaporation the hydrochloride of **4a**.

Anal. Calcd. for C₁₂H₁₆N₆·2HCl (+ 0.4H₂O + 0.05 HCl): C, 44.17; H, 5.82; O, 1.96; N, 25.75; Cl, 22.27. Found: C, 43.91; H, 5.85; N, 25.59; Cl, 22.45.

By neutralization of this hydrochloride with an excess of cold potassium hydroxide solution, one gets, after drying, an excellent yield (> 90%) of azine **4a**, mp >260° (sublimation); Rf = 0.2 (silica gel/ethyl acetate); nmr (dimethylsulfoxide-*d*₆): δ 2.31 (s, 6H, CH₃), 2.5 (s, 6H, CH₃), 7.9 (s, 2H, H-5); ms: 244 (95, M⁺), 229 (100), 122 (88).

From **4f**.

Compound **4f** as the free base (0.124 g, 0.001 mole) was refluxed during 15 hours in methanolic solution with 4 drops (0.004 mole) of hydrazine hydrate. Then the solution was evaporated *in vacuo* and the residue was triturated with boiling cyclohexane, yield >80% of **4a**.

4-Acetyl-1,3-dimethylpyrazole **4b** (R = CH₃).

To a methanolic solution of 1.65 ml (1.43 g, 0.03 mole) methylhydrazine **3b** (R = CH₃) and 6 ml (0.07 mole) concentrated hydrochloric acid is added a methanolic solution of pyrimidine **1** (1.82 g, 0.01 mole). After overnight heating under reflux of the solution, evaporation under vacuum of the solvent one obtains a residue that is dissolved in water then neutralized with a cold solution of potassium hydroxide and extracted several times with different organic solvents (ethyl acetate, chloroform). The combined organic layers are evaporated and the crude product is chromatographed on a silica column with ethyl acetate as the eluent yielding 0.75 g (54%) of **4b** (R = CH₃), mp 44-45° (cyclohexane), Rf = 0.5 (silica gel/ethyl acetate); nmr (dimethylsulfoxide-*d*₆): δ 2.35 (s, 2 × 3H, CH₃-CO, CH₃-3), 3.83 (s, 3H, CH₃-1), 8.35 (s, 1H, H-5); ms: 138 (28, M⁺), 123 (100).

Anal. Calcd. for C₇H₁₀N₂O·H₂O: C, 53.83; H, 7.74; O, 20.48; N, 17.93. Found: C, 53.75; H, 7.73; N, 18.02.

4-Acetyl-3-methyl-1-phenylpyrazole **4b** (R = C₆H₅).

A solution of compound **1** (0.546 g, 0.003 mole), phenylhydrazine (0.648 g, 0.006 mole) in ethanolic hydrochloric medium (pH = 1) was kept at room temperature then water was added to the residue. Several extractions with ethyl acetate of this mixture gave after drying and distillation of the solvent 0.52 g of crude compound **4b** (R = C₆H₅), mp 88° (petroleum ether); ms: 200 (38, M⁺), 185 (100), 77 (42); nmr (dimethylsulfoxide-*d*₆): δ 2.48 (s, 6H, CH₃-3, CH₃-CO), 7.4 to 8.1 (m, 5H, C₆H₅), 9.19 (s, 1H, H-6).

Anal. Calcd. for C₁₂H₁₂N₂O: C, 71.97; H, 6.04; N, 13.98; O, 7.99. Found: C, 71.87; H, 6.03; N, 13.85; O, 7.73.

4-Acetyl-1,3-dimethylpyrazole Azine **4c** (R = CH₃) and 4-Acetyl-1-phenyl-3-methylpyrazole Azine **4c** (R = C₆H₅).

Overnight reflux of an ethanolic solution of pyrazole **4b** with an excess of hydrazine hydrate **3a** (R = H) then distillation of the solvent gave a residue that was suspended in a few milliliters of water then filtered or extracted with ethyl acetate, yield better than 80%.

Compound **4c** (R = CH₃) had mp 205°, Rf, 0.15 (silica gel/ethyl acetate); nmr (dimethylsulfoxide-*d*₆): δ 2.3 (s, 6H, CH₃), 2.44 (s, 6H, CH₃), 3.83 (s, 6H, CH₃-1), 8.15 (s, 2H, H-5); ms: 272 (12, M⁺), 257 (13), 136 (16), 79 (100).

Anal. Calcd. for C₁₄H₂₀N₂O·1.15H₂O: C, 57.37; H, 7.66; O, 6.27; N, 28.67. Found: C, 57.37; H, 7.35; N, 28.81.

Compound **4c** (R = C₆H₅), had mp 154-155°; nmr (dimethylsulfoxide-*d*₆): δ 2.42 (s, 6H, CH₃), 2.58 (s, 6H, CH₃), 7.1 to 8.1 (m, 10H, C₆H₅), 8.9 (s, 2H, H-5); ms: 396 (28, M⁺), 381 (40), 365 (17), 197 (43), 183 (22), 104 (30), 77 (100).

Anal. Calcd. for C₂₂H₂₄N₂: C, 72.7; H, 6.1; N, 21.19. Found: C, 72.55; H, 6.3; N, 21.25.

4-Acetyl-1-amidino-3-methylpyrazole Amidinohydrazone **4d**.

Compound **3c** prepared from aminoguanidine hydrogenocarbonate (3.2 g, 0.024 mole) and concentrated hydrochloric acid (4.2 ml) was mixed with pyrimidine **1** (0.91 g, 0.005 mole) in methanolic solution and refluxed during 4 hours. Upon concentration under vacuum the solution gave a colorless precipitate that was collected and crystallized in methanol, mp >270°, yield 0.75 g; nmr (dimethylsulfoxide-*d*₆): δ 2.4 (s, 3H, CH₃), 2.55 (s, 3H, CH₃), 3.45 (br, 2H, exch), 7.87 (br, 3H, exch), 9.6 (s, 1H, H-5), 10.3

(br, 4H, exch); ms: 222 (27, M⁺), 207 (4), 180 (100), 165 (90); ¹³C nmr (dimethylsulfoxide-*d*₆): 14.85 (CH₃-C3), 16.59 (CH₃-CX-C4), 123.65 (Me-CX-C4), 132.08 (C5), 146.34 (C4), 151.53 (H₂N-C(NH)-N1), 152.81 (CH₃-C3), 156.09 (H₂N-C(NH)-NH-N=).

An additional 30% of the pure pyrazole **4d** was isolated by concentration and cooling of the residual methanolic solution.

Anal. Calcd. for C₈H₁₄N₆·2HCl: C, 32.55; H, 5.46; N, 37.96; Cl, 24.02. Found: C, 32.33; H, 5.55; N, 38.06; Cl, 24.09.

4-Acetyl-3-methylpyrazole Amidinohydrazone **4e** or **6g** (R = CNH-NH₂).

By Acidic Hydrolysis of Pyrazole **4d**.

Refluxing during 16 hours of an aqueous solution of compound **4d** (2 g, 0.0068 mole) in hydrochloric acid (30 ml, 0.36 mole) and extraction with ethyl acetate and ether gave two layers. The aqueous one yielded, after evaporation and crystallization, 1 g (68%) of compound **4e** (hydrochloride); mp >260°; nmr (dimethylsulfoxide-*d*₆): δ 11.35 (s, 1H, exch), 8.3 (s, 1H, H-5), 7.7 and 6.7 (2 br, 5H, exch), 2.50 (s, 3H, CH₃), 2.35 (s, 3H, CH₃); ms: 180 (9, M⁺), 165 (16), 124 (17), 108 (29), 64 (100).

Anal. Calcd. for C₇H₁₂N₆·HCl: C, 38.80; H, 6.05; N, 38.78; Cl, 16.36. Found: C, 38.67; H, 6.06; N, 38.80; Cl, 16.40.

The organic layer gave a very small amount of compound **4f**.

By Basic Hydrolysis of Pyrazole **4d**.

Refluxing of compound **4d** (2 g), sodium hydroxide (2 g) in ethanolic solution during 24 hours, then acidification with hydrochloric acid and work up as in the case previously described, resulted in a very small quantity of compound **4f** and 70% of compound **4e**.

From Compound **4f**.

Compound **4f** (0.48 g, 0.003 mole) was added to a cooled methanolic solution of aminoguanidine hydrogenocarbonate (0.54 g, 0.004 mole) and of 0.7 ml of concentrated hydrochloric acid. After 10 hours refluxing and after complete evaporation of the solvent the dry residue was dissolved in 100 ml of boiling methanol. By cooling at 4° one collected 0.21 g of compound **4e** (hydrochloride). Further concentration of the mother liquors gave additional crops of compound **4e**.

4-Acetyl-3-methylpyrazole **4f**, **6a** (R = H), **6e**.

A solution of hydrazine hydrate (1.65 g, 0.033 mole) in 100 ml ethanol is stirred and cooled at -15°. Dropwise a solution of EMAA (5 g, 0.032 mole) in 100 ml of ethanol was added. As soon as addition of the second solution was finished (90 minutes) the mixture was allowed to each room temperature under stirring. The solvent was removed at room temperature under reduced pressure and the resulting solid was suspended in water and extracted with benzene, ethyl acetate and ethyl ether. From the collected organic layers, distillation of the solvents, acidification with hydrochloric acid dissolution in methanol and precipitation with ether one recovers 2.1 g (42%) of compound **4f** as the hydrochloride (sublimable), Rf 0.3 (silica gel/ethyl acetate), mp 108° dec; nmr (dimethylsulfoxide-*d*₆): δ 2.39 (s, 3H, CH₃), 2.45 (s, 3H, CH₃), 8.30 (s, 1H, H-5); ms: 124 (34, M⁺), 109 (100).

Anal. Calcd. for C₆H₈N₂O·HCl: C, 44.87; H, 5.64; O, 9.96; N, 17.44; Cl, 22.07. Found: C, 44.74; H, 5.70; O, 9.99; N, 17.50; Cl, 22.10.

4-Acetyl-3-methylpyrazole Semicarbazone **4h** (R = CO-NH₂) or **6g** (R = CO-NH₂) and 4-Acetyl-3-methylpyrazole Thiosemicarbazone **4h** (R = CS-NH₂) or **6g** (R = CS-NH₂).

An ethanolic solution of pyrimidine **1** (1.82 g, 0.01 mole) and semicarbazide (or thiosemicarbazide) (0.02 mole) acidified to pH = 1 by addition of a few milliliters of hydrochloric acid was refluxed during 16 hours. Upon cooling at 0° of the solution for several hours a microcrystalline powder separated that was collected and dried (1.625 g). Treatment at 0° with potassium hydroxide gave 1.2 g (66% yield) of compound **4h** (R = CO-NH₂), mp >260° and 1.26 g (64% yield) of compound **4h** (R = CS-NH₂), mp 240°, Rf 0.25 (silica gel/ethyl acetate).

Compound **4h** (R = CO-NH₂) had nmr (dimethylsulfoxide-*d*₆): δ 2.15 (s, 3H, CH₃), 2.40 (s, 3H, CH₃), 6.2 (br, 2H, exch), 7.8 (s, 1H, H-5), 9.1 (br, 1H,

exch), 12.7 (br, 1H, exch); ms: 181 (71, M⁺), 164 (50), 149 (2), 138 (38), 107 (100).

Anal. Calcd. for C₇H₁₁N₅O·0.65H₂O: C, 43.58; H, 6.42; N, 36.30; O, 13.68. Found: C, 43.74; H, 6.43; N, 35.78; O, 13.71.

Compound **4h** (R = CS-NH₂) had nmr (dimethylsulfoxide-d₆): δ 2.25 (s, 3H, CH₃), 2.42 (s, 3H, CH₃), 7.4 (br, 2H, exch), 8.05 (s, 1H, H-5), 8.2 (br, 1, exch), 10.3 (s, 1H, exch); ms: 197 (100, M⁺), 182 (57), 180 (65), 166 (6), 155 (5), 147 (6), 140 (11), 137 (10), 123 (32), 107 (79).

Anal. Calcd. for C₇H₁₁N₅S·0.55H₂O: C, 40.58; H, 5.88; N, 33.80; O, 4.24; S, 15.47. Found: C, 40.78; H, 5.83; N, 33.51; S, 15.39.

5-Acetyl-2-hydrazino-4-methylpyrimidine **5a**.

Excess of hydrazine hydrate (0.32 ml) reacting at room temperature with a methanolic solution of pyrimidine **1** (0.6 g) allows the slow formation of a precipitate of compound **5a**, yield 35%, mp 176°, Rf 0.55 (silica gel/methanol). Purification was sublimation; nmr (dimethylsulfoxide-d₆): δ 2.48 (s, 3H, CH₃), 2.54 (s, 3H, CH₃), 4.4 (br, 2H, exch), 8.82 (s, 1H, H-6), 8.95 (br, 1H, exch); ms: 166 (100, M⁺), 151 (66), 137 (14), 123 (9).

Anal. Calcd. for C₇H₁₀N₄O: C, 50.59; H, 6.06; O, 9.68; N, 33.71. Found: C, 50.44; H, 6.08; O, 9.99; N, 33.81.

5-Acetyl-2-hydrazino-4-methylpyrimidine Hydrazone **5b**.

Hydrazine hydrate (2 ml, 0.04 mole) was added to a solution of compound **5a** (0.997 g, 0.006 mole) in 30 ml of methanol. After refluxing for 24 hours of the solution and partial distillation of the solvent, on cooling one obtained a colorless precipitate of **5b** that was collected, washed with water and crystallized in methanol, yield, 0.37 g (30%), mp 172°; nmr (dimethylsulfoxide-d₆): δ 1.97 (s, 3H, CH₃), 2.32 (s, 3H, CH₃), 4.1 (br, 2H, exch), 6.12 (br, 2H, exch), 8.0 (br, 1H, exch), 8.15 (s, 1H, H-6); ms: 180 (100, M⁺), 165 (18), 149 (34), 134 (7).

Anal. Calcd. for C₇H₁₂N₆: C, 46.65; H, 6.71; N, 46.63. Found: C, 46.5; H, 6.68; N, 45.76.

The same compound may be found from reaction under reflux during 16 hours of a methanolic solution of pyrimidine **1** and a large excess of hydrazine hydrate, yield, 60%.

5-Acetyl-2-methylthio-4-methylpyrimidine Amidinohydrazone **5d**.

Pyrimidine **1** (1.82 g, 0.01 mole) reacting with an excess of amidinohydrazone hydrogenocarbonate (3 g) in ethanolic solution acidified to pH 2 or 3 with concentrated hydrochloric acid and left at room temperature for a week gives after removal of the solvent at room temperature a microcrystalline powder. After crystallization in ethanol the yield is 2 g (84%) of yellow needles of **5d**, mp 144°; nmr (dimethylsulfoxide-d₆): δ 2.25 (s, 3H, S-CH₃), 2.55 (s, 6H, CH₃), 5.55 to 5.80 (br d, 4H, exch), 8.50 (s, 1H, H-6); ms: 239 (26, M⁺ + 1), 238 (9, M⁺), 237 (26), 223 (100), 195 (26), 181 (60), 149 (23).

Anal. Calcd. for C₉H₁₄N₆S·HCl·0.2H₂O: C, 38.83; H, 5.57; O, 1.14; N, 30.18; S, 11.51; Cl, 12.73. Found: C, 38.72; H, 5.60; N, 30.10; S, 11.50; Cl, 12.75.

The same compound may be obtained in a 67% yield besides a small amount of compound **4d** if the mixture of the same reagents is refluxed for 90 minutes in a solution of benzene, concentrated hydrochloric acid, and methanol under a Dean-Stark apparatus in order to discard water from the medium, by azeotropic distillation.

5-Acetyl-4-methyl-2-methylthiopyrimidine Semicarbazone **5e** (R = CO-NH₂) and 5-Acetyl-4-methyl-2-methylthiopyrimidine Thiosemicarbazone **5e** (R = CS-NH₂).

A solution of pyrimidine **1** (0.95 g, 0.005 mole), semicarbazide hydrochloride (or thiosemicarbazide) (0.01 mole) in 100 ml methanol acidified to pH = 1 with concentrated hydrochloric acid was stirred at room temperature for one week. Excess solvent was evaporated at room temperature under vacuum and the resulting precipitate was collected, washed with a small amount of cold water, and recrystallized in boiling methanol to give more than 80% of product **5e**.

Compound **5e** (R = CO-NH₂) had mp 232°; nmr (dimethylsulfoxide-d₆): δ 2.17 (s, 3H, CH₃), 2.50 (s, 6H, 2CH₃), 6.40 (br, 2H, exch), 8.60 (s, 1H, H-6), 9.50 (br, 1H, exch); ms: 239 (87, M⁺), 222 (8), 217 (4), 195 (35), 181

(100), 165 (31), 149 (99).

Anal. Calcd. for C₉H₁₃N₅OS: C, 45.17; H, 5.47; N, 29.26; O, 6.68; S, 13.39. Found: C, 45.10; H, 5.61; N, 29.28; O, 7.01; S, 13.48.

Compound **5e** (R = CS-NH₂) had mp 217°; nmr (dimethylsulfoxide-d₆): δ 2.30 (s, 3H, CH₃), 2.53 (s, 6H, 2CH₃), 8.10 (br, 2H, exch), 8.62 (s, 1H, H-6), 10.50 (br, 1H, exch); ms: 255 (80, M⁺), 240 (16), 238 (30), 222 (14), 213 (46), 195 (18), 181 (100).

Anal. Calcd. for C₉H₁₃N₅S₂·0.1H₂O: C, 42.03; H, 5.17; O, 0.62; N, 27.23; S, 24.93. Found: C, 42.22; H, 5.28; N, 26.95; S, 24.79.

4-Acetyl-1,5-dimethylpyrazole **6a** (R = CH₃) and 4-Acetyl-5-methyl-1-phenylpyrazole **6a** (R = C₆H₅).

A solution of EMAA **2** (3 g, 0.019 mole) in 50 ml of methanol was stirred at -15° during the slow addition of a cooled methanolic solution of hydrazine **3d** (0.02 mole) and 4 ml of concentrated hydrochloric acid. Stirring was continued at room temperature during half an hour in one case (R = CH₃) and 7 hours in the other case (R = C₆H₅). After removal at room temperature of the solvent the resulting mixture was basified with a cold aqueous solution of potassium hydroxide. The precipitate, in the case of **6a** (R = C₆H₅) was collected and washed with water. The alkaline solution was thoroughly extracted several times with ethyl acetate. From the organic layers after the usual treatment one obtains the pyrazole **6a**.

Compound **6a** (R = CH₃) was obtained in a yield greater than 90%; mp 43-44° (cyclohexane); nmr (dimethylsulfoxide-d₆): δ 2.36 (s, 3H, CH₃), 2.48 (s, 3H, CH₃), 3.75 (s, 3H, CH₃), 7.9 (s, 1H, H-3); ms: 138 (26, M⁺), 123 (100).

Anal. Calcd. for C₇H₁₀N₂O: C, 60.85; H, 7.29; N, 20.27; O, 11.57. Found: C, 60.53; H, 7.07; N, 20.14.

Compound **6a** (R = C₆H₅) was obtained in a yield of 68%, Rf 0.8 (silica gel/ethyl acetate), mp 120° (cyclohexane) (107-108° as quoted by Claisen [9]); nmr (dimethylsulfoxide-d₆): δ 2.48 (s, 3H, CH₃), 2.53 (s, 3H, CH₃), 7.55 (s, 5H, C₆H₅), 8.24 (s, 1H, H-5); ms: 200 (39, M⁺), 185 (100), 77 (32).

4-Acetyl-1,5-dimethylpyrazole Azine **6b** (R = CH₃).

An aqueous solution of dimethylpyrazole **6a** (R = CH₃) (1 g, 0.0072 mole) and hydrazine hydrate (1.5 ml, 0.03 mole) were refluxed during 6 hours. Water was discarded under reduced pressure and the residue suspended in ether was collected and dried, yield, 0.8 g (80%) of compound **6b** (R = CH₃), mp 238°, Rf 0.17 (silica gel/ethyl acetate), yellow colour; nmr (dimethylsulfoxide-d₆): δ 2.25 (s, 6H, 2CH₃), 2.55 (s, 6H, 2CH₃), 3.76 (s, 6H, 2CH₃), 7.70 (s, 2H, H-3); ms: 272 (60, M⁺), 258 (63), 136 (100), 121 (43), 80 (73).

Anal. Calcd. for C₁₄H₂₀N₄O·0.25H₂O: C, 60.73; H, 7.46; O, 1.44; N, 30.35. Found: C, 60.42; H, 7.24; N, 30.61.

4-Acetyl-5-methyl-1-phenylpyrazole Azine **6b** (R = C₆H₅).

An ethanolic solution of compound **6a** (R = C₆H₅) (0.5 g, 0.0025 mole) and hydrazine hydrate (1 ml, 0.02 mole) were refluxed for 10 hours. Then the solvent was distilled under vacuum and the residue was taken up in water, acidified to pH = 1 with hydrochloric acid. The resulting solution was extracted several times with ethyl acetate. The combined organic layers were evaporated leaving a yellow residue, of, mainly, azine **6b** (R = C₆H₅). An aliquot was suspended and washed with ether for analytical purposes, mp 184°, Rf 0.95 (silica gel/ethyl acetate), nmr (dimethylsulfoxide-d₆): δ 2.37 (s, 6H, 2CH₃), 2.60 (s, 6H, 2CH₃), 7.64 (s, 10H, 2C₆H₅), 8.17 (s, 2H, H-3); ms: 396 (5, M⁺), 381 (4), 200 (40), 185 (100), 77 (80).

Anal. Calcd. for C₂₄H₂₂N₆·0.2H₂O: C, 72.04; H, 6.14; O, 0.79; N, 21.00. Found: C, 71.82; H, 6.20; N, 21.10.

4-Acetyl-5-methyl-1-phenylpyrazole Phenylhydrazone **6c**.

A solution of compound **6a** (R = C₆H₅) (0.5 g, 0.0025 mole) and phenylhydrazine **3b** (R = C₆H₅) (1 ml, 0.01 mole) in ethanol were refluxed during 6 hours. Then the solvent was completely removed and the residue was suspended in water and acidified to pH = 1 with hydrochloric acid. The precipitate was collected and crystallized in boiling ethanol, yield, 0.6 g (83%) of compound **6c**, mp 188° Rf 0.85 (silica gel/ethyl acetate); nmr (dimethylsulfoxide-d₆): δ 2.28 (s, 3H, CH₃), 2.58 (s, 3H, CH₃), 7.2 to

7.6 (m, 10H, arom), 7.87 (s, 1H, H-3), 9.03 (s, 1H, NH exch); ms: 290 (100, M⁺), 272 (2), 198 (27), 183 (7), 132 (11), 91 (48).

Anal. Calcd. for C₁₈H₁₈N₄: C, 74.45; H, 6.24; N, 19.29. Found: C, 74.74; H, 6.35; N, 19.36.

4-Acetyl-1-amidino-5-methylpyrazole **6d** (R = CNH-NH₂).

A solution of aminoguanidine hydrogenocarbonate (1.36 g, 0.01 mole) in water (2.4 ml) and concentrated hydrochloric acid (1.7 ml, 0.02 mole) were added dropwise to a cooled (15°) methanolic solution of EMAA **2** (1.56 g, 0.01 mole), then the mixture was stirred 3 hours at room temperature. The solvent was distilled at low temperature and the residue was neutralized with sodium hydrogenocarbonate then extracted with ethyl acetate. The evaporation of the organic layer was followed by acidification with hydrochloric acid in ethanol of the solid, subsequent precipitation with ether and trituration with boiling methanol gave 0.47 g (23%) of product **6d**, sublimes and decomposes at 180°, Rf 0.66 (silica gel/methanol); nmr (dimethylsulfoxide-d₆): δ 2.55 (s, 3H, CH₃), 2.8 (s, 3H, CH₃), 3.6 (br, 1H, exch), 8.5 (s, 1H, H-3), 10.1 (br, 3H, exch); ms: 166 (7.5, M⁺), 124 (50), 109 (100).

Anal. Calcd. for C₇H₁₀N₄O·HCl·0.25H₂O: C, 40.58; H, 5.59; O, 9.65; N, 27.04; Cl, 17.11. Found: C, 40.90; H, 5.42; O, 9.75; Cl, 17.19.

4-Acetyl-1-carbamoyl-5-methylpyrazole **6d** (R = CO-NH₂).

A cooled methanolic solution of semicarbazide hydrochloride **3d** (R = CO-NH₂) (4.4 g, 0.04 mole) and concentrated hydrochloric acid (1 ml) were slowly added into a cooled (15°) methanolic solution of EMAA **2** (6 g, 0.038 mole). The slight precipitate that appeared was dissolved with the addition of a few milliliters of water then stirring was continued at room temperature for a few hours. The new precipitate was collected, washed with ice-cold water and dried under vacuum at 100°, yield, 5 g (81%). This product may be purified by chromatography on a column of silica gel with ethyl acetate, Rf 0.9 (silica gel/ethyl acetate), mp 180° (decomposition begins at 160°). In the mother liquors the same compound **6d** (R = CO-NH₂) may be characterised by besides a small amount of compound **6e** (or **4f**); nmr (dimethylsulfoxide-d₆): δ 2.46 (s, 3H, CH₃), 2.82 (s, 3H, CH₃), 7.93 (b4, 2H, exch), 8.23 (s, 1H, H-3); ms: 167 (9, M⁺), 124 (30), 109 (100).

Anal. Calcd. for C₇H₈N₃O₂: C, 50.29; H, 5.42; O, 19.14; N, 25.13. Found: C, 50.20; H, 5.45; O, 19.18; N, 25.10.

4-Acetyl-1-amidino-5-methylpyrazole Amidinohydrazone **6f** (R = CNH-NH₂).

An aqueous solution of aminoguanidine hydrochloride **3c** was added dropwise to a cooled (-15°) stirred methanolic solution of FMAA **2** (1.5 g, 0.01 mole). The stirred solution was kept at room temperature for one day. The colorless precipitate was collected, washed with methanol and dried, yield, 1.1 g (36%), mp >260°; nmr (dimethylsulfoxide-d₆): δ 2.39 (s, 3H, CH₃), 2.71 (s, 3H, CH₃), 7.88 (br, 4H, exch), 8.41 (s, 1H, H-3), 10.8 (br, 5H, exch); ms: 222 (2, M⁺), 207 (1), 180 (90), 165 (100), 108 (55).

Anal. Calcd. for C₉H₁₄N₆·2HCl·0.88H₂O: C, 30.89; H, 5.75; O, 4.52; N, 36.02; Cl, 22.79. Found: C, 31.03; H, 5.84; N, 35.92; Cl, 22.58.

The methanolic mother liquors contain additional quantities of compound **6f** (R = -CNH-NH₂), and no trace of its isomer **4d** (proved by nmr study); ¹³C nmr (dimethylsulfoxide-d₆): 12.59 (CH₃-C5), 17.14 (CH₃-CX-C4), 122.1 (Me-CX-C4), 140.9 (CH₃-C5), 143.7 (C3), 147.0 (C4), 153.9 (H₂N-C(NH)-N1), 156.2 (H₂N-C(NH)-NH-N=).

4-Acetyl-1-carbamoyl-5-methylpyrazole Semicarbazone **6f** (R = -CO-NH₂).

A cooled (-15°) aqueous solution of semicarbazide hydrochloride (2.8 g, 0.025 mole) and concentrated hydrochloric acid (1 ml, 0.012 mole) was

slowly poured into a stirred cooled (-15°) methanolic solution of EMAA **2** (1.56 g, 0.01 mole). The resulting mixture was stirred at room temperature for a few hours, then the precipitate was collected, washed with hot ethanol, and dried, yield, 1 g (44%) of compound **6f** (R = -CO-NH₂), mp 234°, insoluble in dimethylsulfoxide; ms: 224 (1, M⁺), 181 (21), 164 (12), 138 (11), 120 (12), 107 (48), 43 (100).

Anal. Calcd. for C₈H₁₂N₆O₂: C, 42.85; H, 5.39; N, 37.48. Found: C, 42.90; H, 5.43; N, 37.40.

This compound suspended in a cold solution of potassium hydroxide and stirred at room temperature during one day gave a precipitate of compound **4h** (R = -CO-NH₂), **6g** (R = -CO-NH₂).

4-Acetyl-5-methyl-1-thiocarbamoylpyrazole Thiosemicarbazone **6f** (R = -CS-NH₂).

A solution of thiosemicarbazide **3d** (R = CS-NH₂) (3.6 g, 0.04 mole) and concentrated hydrochloric acid, 2 ml in 250 ml of methanol was poured into a cooled stirred solution of EMA **2** (3 g, 0.02 mole) in 50 ml of methanol then the mixture was left under stirring at room temperature for 2 hours. One obtained 3.5 g of a compound, m/e = 256, Rf 0.75 (silica gel/ethyl acetate), mp 240°, spattering.

Attempts at crystallization of this compound in boiling water or both alcohols transformed it into **6g** (R = -CS-NH₂) (shown by tlc).

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