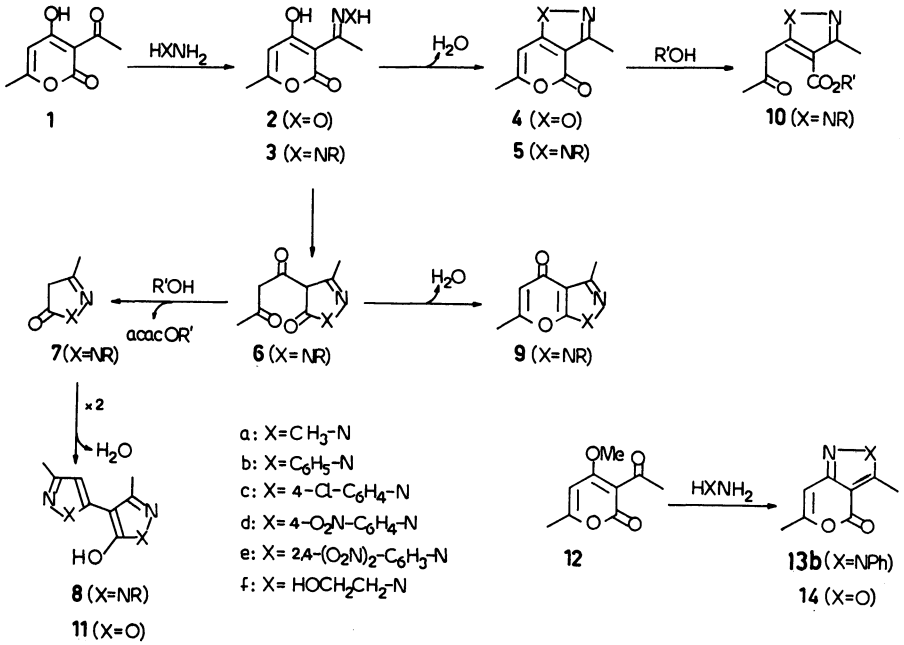
# Synthesis of Pyrano[4,3-*c*]pyrazol-4(1*H*)-ones and -4(2*H*)-ones from Dehydroacetic Acid. Homo- and Heteronuclear Selective NOE Measurements for Unambiguous Structure Assignment

Albert CANTOS, Pedro de MARCH, Marcial MORENO-MAÑAS,* Anna PLA, Francisco SANCHEZ-FERRANDO,* and Albert VIRGILI
Departament de Química. Universitat Autnoma de Barcelona, Campus de Bellaterra, 08193 Barcelona, Spain
(Received October 20, 1986)

Cyclization of dehydroacetic acid *N*-substituted hydrazones furnished 1-substituted 3,6-dimethylpyrano-[4,3-*c*]pyrazol-4(1*H*)-ones, together with varying amounts of *N,N'*-disubstituted 5-hydroxy-3-methyl-4-(3-methyl-1*H*-pyrazol-5-yl)-1*H*-pyrazoles. The same pyranopyrazolones were obtained regioselectively without side reactions from *N*-alkylhydrazines and 4-chloro-3-(1-chlorovinyl)-6-methyl-2*H*-pyran-2-one, ("Dehydroacetchlorid"), while *N*-arylhydrazines gave the 2-aryl-3,6-dimethylpyrano[4,3-*c*]pyrazol-4(2*H*)-ones. NMR NOE methods, including long-range selective heteronuclear $^{13}C\{^1H\}$ NOE enhancement measurements, allowed unambiguous distinction between -4(1*H*)-ones and -4(2*H*)-ones.

The reactions of dehydroacetic acid **1** and derivatives with hydroxylamine or hydrazines are a rich source of several types of heterocycles[1] (Scheme 1). Thus, the initially formed oxime **2** or hydrazones **3** have been converted into 3,6-dimethyl-4*H*-pyrano[3,4-*d*]isoxazol-4-one (**4**)[2] or into pyrano[4,3-*c*]pyrazol-4(1*H*)-ones (**5**),[3] 4-acetoacetyl-2,4-dihydro-5-methyl-3*H*-pyrazol-3-ones (**6**),[4] 2,4-dihydro-5-methyl-3*H*-pyrazol-3-ones (**7**)[5] or their formal condensation dimers 5-hydroxy-3-methyl-4-(3-methyl-1*H*-pyrazol-5-yl)-1*H*-pyrazoles (**8**),[3,4] pyrano[2,3-*c*]pyrazol-4(1*H*)-ones (**9**),[4] and 5-(2-oxopropyl)-1*H*-pyrazole-4-carboxylates (**10**).[3b,c] 4-(5-Isoxazolyl)isoxazole (**11**) has also been reported[6] from reaction of **1** with hydroxylamine. Even the formation of 5-anilino-1,5-dihydro-3,6-dimethyl-1-phenyl-4*H*-pyrazolo[4,3-*c*]pyridin-4-one from **1** and phenylhydrazine was once claimed,[7] although this reaction was later shown[4] to afford only **8b**. Depending upon the reaction conditions, most compounds **5**—**10** can be obtained directly from **1** and hydrazines, usually as mixtures with the corresponding hydrazones **3**.[3c] Furthermore, reaction of the methyl ether of dehydroacetic acid (**12**) with phenylhydrazine or hydroxylamine gives 3,6-dimethyl-2-phenylpyrano[4,3-*c*]pyrazol-4(2*H*)-one (**13b**)[3c,8] or 3,6-dimethyl-4*H*-pyrano[4,3-*c*]isoxazol-4-one (**14**)[3c,8] while Oppenheim's "Dehydroacetchlorid,"[9] of hitherto-unknown constitution, has long been known[9b] to react with phenylhydrazine giving an as yet unidentified isomer, mp 203 °C, of **5b**.

Clearly, some sort of control on regioselectivity is desirable for this manifold of reactions and in general in pyrazole and isoxazole syntheses. Thus, in the related case of β-substituted enones, the treatment with hydroxylamine under carefully controlled conditions has been reported to afford regioselectively the isomeric 3,5-disubstituted isoxazoles through pH control of the more nucleophilic center in hydroxylamine.[10a] Also, a regioselective synthesis of 3,5-disubstituted




Scheme 1.

isoxazoles based on the reactivity of 3-methylthio-2-buten-1-ones has been recently reported.[10b]

We herein report on: i) The synthesis of several new hydrazones **3**, their cyclization to pyranopyrazolones **5**, and their conversion to pyrazolylpyrazoles **8**; ii) the identification of Oppenheim's "Dehydroacetchlorid" as 4-chloro-3-(1-chlorovinyl)-6-methyl-2*H*-pyran-2-one (**15**) and its regioselective conversion into pyranopyrazolones **5** or **13**; iii) an NMR study of some of these compounds, mainly based on NOE measurements, which allows unambiguous structure assignment between pairs of possible isomers.[11]

## Results and Discussion

Reaction of **1** with hydrazines in methanol yielded the corresponding hydrazones **3a—e** in fair to good yields (Table 1). The configuration of the C=N double bond was not determined. Nevertheless, hydrazones **3a—c** were cyclized to the corresponding pyrano[4,3-*c*]pyrazol-4(1*H*)-ones **5a—c** (Table 2), although the very insoluble hydrazones **3d—e** could not be cyclized, due to the very low nucleophilicity of the aryl-bound nitrogen atom.

Formation of pyrazolylpyrazole **8c** upon treatment of hydrazone **3c** with aqueous HCl in DME under reflux has precedent in the known[3a] formation of **8b**, together with **5b**, when **1** is reacted with two equivalents of phenylhydrazine hydrochloride. Thus, a possible mechanism through **6c** can be envisaged (Scheme 2, path b). However, we have been unable to find the 3,4′-bipyrazoles **16**. (Scheme 2, path a). Therefore, an alternative mechanism through pyrazolone **7c** cannot be excluded, since its formation from **6c** involves a simple retro-Claisen condensation and the closely related compound **7b** (Ar=$C_6H_5$) is known[13] to yield **8b** upon heating.

In the present work, reaction or **1** with two equivalents of either methylhydrazine or (2-hydroxyethyl)-hydrazine also gave the corresponding pyrazolylpyrazoles **8a** and **8f** (Table 3).

NMR experiments, summarized below, showed convincingly, that the product from the first reaction of Table 3 was indeed **8a**, rather than **16a**. The 80 MHz $^1$H NMR spectrum of **8a** in $CDCl_3$ showed the presence of several unresolved long range couplings, which were uncovered by resolution enhancement via gaussian multiplication and zero-filling of the FID prior to Fourier transformation.[14] In this way, the assignments shown in Table 4 were made. Double irradiation experiments, also shown in Table 4, confirmed these assignments.

In order to complete the characterization of **8a**, a homonuclear $^1$H{$^1$H} NOE experiment was performed, using the NOE difference technique.[15] Irradiation of the $N_{1'}$-methyl at $\delta$ 3.51 gave about 1% increase in the signals of the C-methyl groups, a result which rules out constitution **16a**, for which a much more significant (≃15%) increase of the adjacent C-methyl group, at $\delta$ 2.06, was expected. The only clear increase from this NOE difference experiment was a 10% enhancement of the 5-hydroxyl proton, at $\delta$ 8.5—9.5, thus showing that the conformation of **8a** is *seqcis*, and not *seqtrans* (Scheme 3), possibly due to steric hindrance between both methyl groups in the latter.

A similar conclusion was drawn for compound **8c**,

Table 1. Preparation of Oxime **2** and Substituted Hydrazones **3** of Dehydroacetic Acid[a]

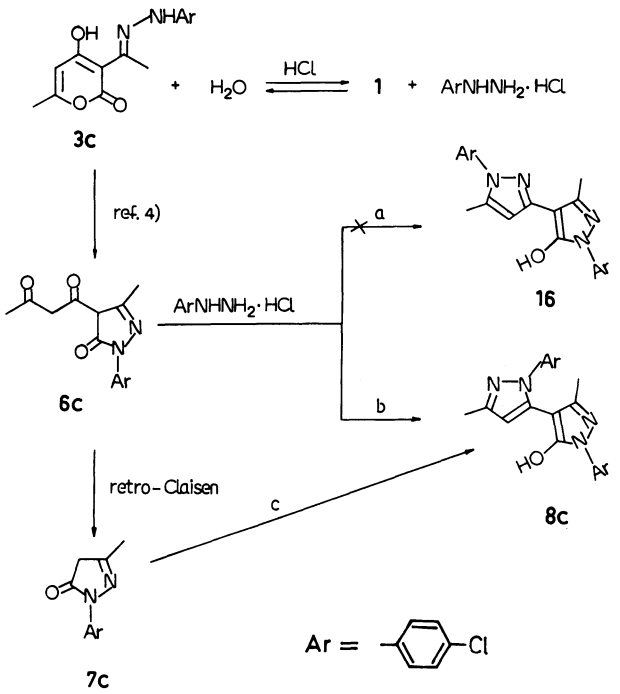
| Product | X | Molar ratio $HXNH_2$/**1** | Condition | Yield % | Mp $\theta_m$/°C |
|---|---|---|---|---|---|
| **2** | O | 2.1[b] | R.t., 17 h | 76 | 171—173[f] |
| **3a** | $CH_3N$ | 1.1[c] | R.t., 25 h[d] | 50[e] | 100—102 |
| **3b** | $C_6H_5N$ | 1.1[c] | R.t., 1 h | 91 | 211—212[g] |
| **3c** | 4-$ClC_6H_4N$ | 1.1[b] | R.t., 15 h | 95 | 188—190 |
| **3d** | 4-$NO_2$-$C_6H_4N$ | 1.2[c] | Refl., 16 h | 93 | 220—223 |
| **3e** | 2,4-$(NO_2)_2C_6H_3N$ | 1.2[c] | Refl., 21 h | 35 | 228—231 |

a) A 0.1 M (1 M=1 mol dm$^{-3}$) solution of **1** in MeOH was used, unless otherwise stated. b) A mixture of $HXNH_2$·HCl and 10% excess sodium acetate trihydrate was used. c) Free $HXNH_2$ was used. d) Solvent: DME. e) Pyrazolylpyrazole **8a** was detected in the mother liquor. f) Lit, 171—173°C (Ref. 6). g) Lit, 211—212°C (Ref. 12).

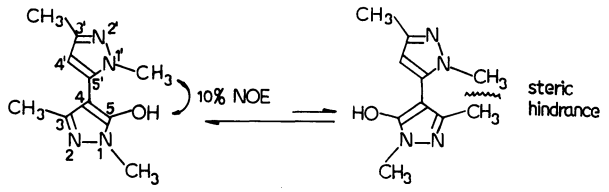
Table 2. Cyclization of Hydrazones **3**

| Starting material | Reagent | Reaction condition | Product | Yield/% | Mp $\theta_m$/°C |
|---|---|---|---|---|---|
| **3a** | 1 equiv 1M HCl | DME, r.t., 23 h | **5a** | 73 | 152—154 |
| **3b** | Cat. TsOH | Xylene, reflux, 12 h | **5b**[a,b] | 33 | 156—157[d] |
| **3c** | 1.2 equiv 1M HCl | DME, reflux, 49 h | **5c**[c] | 18 | 220—222 |

a) Neither Mitsunobu's reagent ($EtO_2CN$=$NCO_2Et$/$PPh_3$) nor $POCl_3$ under reflux achieved the desired increase in the yield of **5b** and/or decrease in by-product **9b**. b) Also obtained was a second product, in 30% yield, identified as 3,6-dimethyl-1-phenylpyrano[2,3-*c*]pyrazol-4(1*H*)-one, **9b**, mp 150°C (lit, 150°C (Ref. 4)). c) Also obtained was pyrazolylpyrazolone **8c**, mp 272—275°C, in 17% yield. See text for characterization. d) Lit, 156—157°C (Ref. 3b).



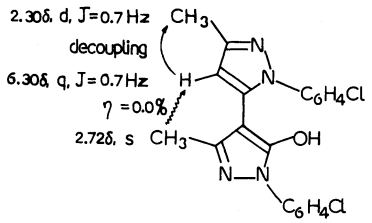

Scheme 2.




Scheme 3.

in which irradiation of the $C_3$-methyl protons at $\delta$ 2.72 gave no significant increase for any of the *p*-chlorophenyl singlets. The results are summarized in Scheme 4.

(2-Hydroxyethyl)hydrazine-derived pyrazolylpyrazole **8f** could not be structurally assigned by NOE measurements. However, the close similarity between its spectra and those of **8a** points to a common structural type for both compounds (See experimental). In particular, the UV spectrum of **8a** shows peaks at 210, 226, and 260 nm, while **8f** shows 207, 226, and 258 nm. Also, the aromatic carbons exhibit very similar chemical shifts in the $^{13}C$ NMR spectra of both compounds.




Scheme 4.

**Identification and Reactions of Oppenheim's "Dehydroacetchlorid": Preparation of 1-Alkyl-3,6-dimethylpyrano[4,3-*c*]pyrazol-4(1*H*)-ones (5), and 2-Aryl-3,6-dimethylpyrano[4,3-*c*]pyrazol-4(2*H*)-ones (13).** As early as 1876, Oppenheim and Precht reported[9a] that reaction of **1** with phosphoryl chloride and phosphorus pentachloride gave a compound, $C_8H_6O_2Cl_2$, mp 101 °C, which they named "Dehydroacetchlorid." We have now found, that reaction of **1** with phosphoryl chloride gives 4-chloro-3-(1-chlorovinyl)-6-methyl-2*H*-pyran-2-one (**15**), mp 100 °C, and therefore we propose this constitution for "Dehydroacetchlorid." Constitution **15** is clear from elemental analysis and spectral data (see Experimental). Furthermore, in 1890 Feist reported[9b] that reaction of **15** with phenylhydrazine gave an unidentified compound, mp 203 °C, isomeric with **5b**. We have repeated this reaction and, in our hands, the resulting compound showed mp 209—210 °C. This compound was identical with **13b**, previously obtained by a Russian group[3c,8] from reaction of 3-acetyl-4-methoxy-6-methyl-2*H*-pyran-2-one (**12**) with phenylhydrazine. A comparison between the

Table 3. Preparation of Pyrazolylpyrazoles **8**

| Starting material | Reagent | Reaction condition | Product | Yield/% | Mp $\theta_m$/°C |
|---|---|---|---|---|---|
| **1** | $MeNHNH_2$ (2 equiv) | DME, r.t., 47 h | **8a** | 33 | 203—204 |
| **3c** | 1M aq HCl (1.2 equiv) | DME, reflux, 49 h | **8c**[a] | 17 | 272—275 |
| **1** | $HOCH_2CH_2NHNH_2$ (2.5 equiv) | DME, reflux, 91 h | **8f** | 38 | 79—82 |

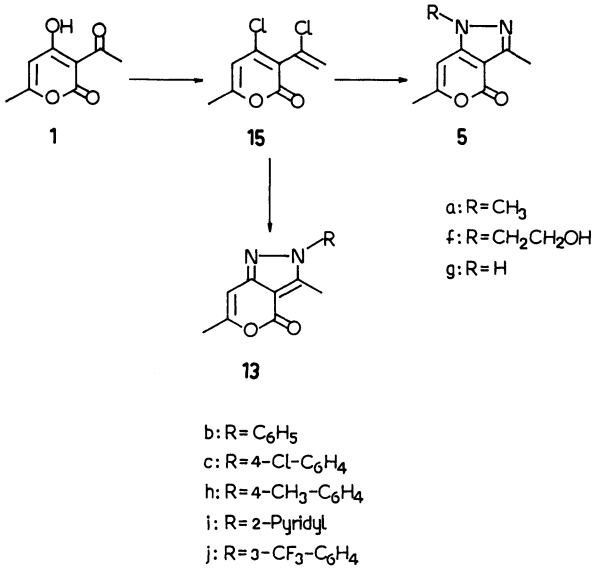
a) See also Table 2, entry 3.

Table 4. The Assigned 80 MHz $^1H$ NMR Spectrum of **8a**, 50 mM in $CDCl_3$[a]

| Proton | $\delta$/ppm | Mult. | $J$/Hz | Decouplin and NOE |
|---|---|---|---|---|
| $N_1$-Me | 3.63 | q | 0.3 | |
| $C_3$-Me | 2.01 | q | 0.3 | Note[b] |
| $C_5$-OH | 8.5—9.5 | broad | — | Note[c] |
| $N_{1'}$-Me | 3.51 | q | 0.3 | |
| $C_{3'}$-Me | 2.06 | dq | 0.6; 0.3 | Note[d,e] |
| $C_{4'}$-H | 5.78 | q | 0.6 | |

a) See Scheme 3 for numbering. b) Upon irradiation at $\delta$ 3.63 collapses to a singlet. c) Upon low power presaturation at $\delta$ 3.51 under NOE difference conditions, this signal shows a 10% enhancement in its integrated area. d) Collapses to a quartet, $J$=0.3 Hz, when decoupling from $C_{4'}$-H at $\delta$ 5.78. e) Collapses to a doublet, $J$=0.6 Hz, when decoupling from $N_{1'}$-Me at $\delta$ 3.51.

reactions of **1**, **12**, and **15** with hydroxylamine or phenylhydrazine is worth here. Thus, **1** gives only products derived from initial attack on the side-chain carbonyl group, and therefore **1** can be converted into the fused heterocycles **4** and **5**, but not into the isomeric **13** and **14**. However, the increased electrophilicity of C-4 in both **12** and **15** opens up the way to **13** and **14** via




Scheme 5.

initial attack of the nucleophile on the now more reactive C-4. This point was confirmed by reaction of **15** with several arylhydrazines (Scheme 5), which furnished the expected 3,6-dimethyl-2-arylpyrano[4,3-*c*]pyrazol-4(2*H*)-ones (**13**) in fair to good yields (Table 5). Furthermore, reaction of **15** with alkylhydrazines gave the 3,6-dimethyl-1-alkylpyrano[4,3-*c*]pyrazol-4(1*H*)-ones (**5**) (Table 5), i.e., the products also expected from initial attack of the now more nucleophilic, substituted nitrogen of the hydrazine on C-4 of the pyrone ring of **15**.

**Distinguishing between 1-Substituted 5 and 2-Substituted Pyranopyrazoles 13: NOE Measurements.** Throughout the present work, we felt the need for a quick and reliable method for ascertaining the constitution of new pyranopyrazolones as **5** or **13** in an unambiguous way. Since the new compounds were crystalline solids, X-ray diffraction analysis was one possibility, but we were seeking for a faster, more versatile method. The new 2-D NMR techniques[16] were also out of question, because usually they require large amounts of sample and long measuring times. Hopefully, homonuclear $^1H\{^1H\}$ NOE measurements[17] particularly in the useful NOE difference mode,[18] are very helpful for the constitutional assignment of simple fused heterocycles.[15] Thus, in 3,6-dimethylpyrano[4,3-*c*]pyrazol-4(1*H*)-ones (**5**), the group bound to N-1 has

Table 5. Reactions of **15** with Hydrazines, $RNHNH_2$

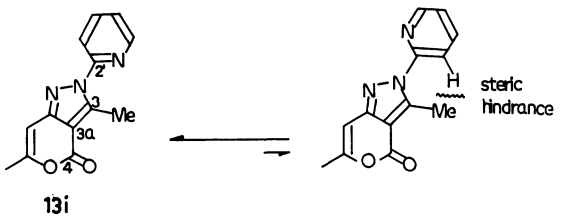
| R | Equiv hydraz. | Reaction condition | Product | Yield/% | Mp $\theta_m$/°C |
|---|---|---|---|---|---|
| H | 4.1[a] | EtOH, reflux, 1.75 h | **5g** | 21 | 192—194 |
| $CH_3$ | 3.1[b] | DME, r.t., 20 h | **5a** | 40 | 152—154 |
| $HOCH_2CH_2$ | 3.6[b] | MeOH, r.t., 40 h | **5f** | 81 | 144—146 |
| $H_2NCO$ | 3.2[c] | EtOH, reflux, 21 h | **5g**[d] | 49 | 192—194 |
| $C_6H_5$ | 4.9[b] | DME, reflux, 54 h | **13b** | 53 | 209—210[f] |
| 4-$ClC_6H_4$ | 3.1[c] | MeOH, reflux, 91 h | **13c** | 83 | 179—182 |
| 4-$MeC_6H_4$ | 3.2[c] | MeOH, reflux, 66 h | **13h** | 58 | 172—173 |
| 2-Pyridyl | 3.1[b] | MeOH, reflux, 39 h | **13i** | 33 | 154—155 |
| 3-$CF_3$-$C_6H_4$ | 3.2[b] | MeOH, reflux, 66 h | **13j** | 76 | 156—157 |
| 4-$NO_2C_6H_4$ | 3.1[b] | DME, reflux, 20 h | None[e] | | |

a) Hydrazine hydrate (98%) was used. b) The substituted hydrazine was used as the free base. c) A mixture of $RNHNH_2 \cdot HCl$ and 1.2 equiv $NaOAc \cdot 3H_2O$ in MeOH was used. d) A second solid, mp 248—250 °C, identified as 1,2-hydrazinedicarboxamide, was also obtained from this reaction. e) Starting materials were recovered unaltered due to the poor nucleophilicity of 4-nitrophenylhydrazine. f) Lit, 210 °C (Refs. 3c and 8).

Table 6. Homonuclear NOE Enhancements in Pyrano[4,3-*c*]pyrazol-4(1*H*)-ones **5** and **13**[a]

| Compound | Irradiated proton | | Enhanced proton | | $\eta$/% |
|---|---|---|---|---|---|
| | Numbering | $\delta$/ppm | Numbering | $\delta$/ppm | |
| **5a** | $N_1$-Me | 3.9 | $H_7$ | 6.15 | 4.4 |
| **5c** | $H_{Ar}$ | 7.6 | $H_7$ | 6.3 | 10.0 |
| **5f** | $H_7$ | 6.2 | $N_1$-$CH_2$ | 4.1 | 1.7 |
| | | | $C_6$-Me | 2.3 | 1.0 |
| **13b** | $C_3$-Me | 2.8 | $H_{Ar}$ | 7.5 | 5.3 |
| **13c** | $C_3$-Me | 2.8 | $H_{Ar}$ | 7.5 | 5.0 |
| **13h** | $H_{Ar}$ | 7.3 | $C_3$-Me | 2.75 | 2.5 |
| **13i** | $C_3$-Me | 3.1 | ·····None····· | | |
| | $H_7$ | 6.25 | $C_6$-Me | 2.3 | 1.6 |
| **13j** | $C_3$-Me | 2.8 | $H_{Ar}$ | 7.6—7.8 | 4.8 |

a) Determined on 10 mM solutions in $CDCl_3$, using the NOE difference technique.




Scheme 6.

its protons close to H-7, while in the isomeric -4(2*H*)-ones the N-2 bound group is close to the C-3 methyl group. A series of homonuclear $^1H\{^1H\}$ NOE difference experiments, summarized in Table 6, confirmed this expectations, and provided clear-cut proof for structures **5** and **13**. One exception was compound **13i**, for which no homonuclear NOE enhancements were found besides the trivial $C_6$-Me{$H_7$}. The lack of NOE on any pyridine proton upon irradiation at the C-3 methyl protons was taken as evidence for conformation *seqtrans*, rather than *seqcis* (Scheme 6).

Finally, proof for constitution **13i** rather than **5i** was obtained by means of the recently reported technique[19,20] of long range, selective heteronuclear $^{13}C\{^1H\}$ NOE measurements. Thus, the assigned $^{13}C$ NMR spectrum of **13i** is given in Table 7. As shown in Scheme 6, the C-3 methyl protons are close to four quaternary carbons, namely C-3, C-3a, and C-4 of the pyranopyrazole nucleus, as well as, to the C-2′ carbon of the pyridine substituent. Therefore, low power preirradiation of the C-3 methyl protons should result in a NOE enhancement of these four quaternary carbons.[19,20]

As shown in Table 7, this was indeed the case. This result, which proves constitution **13i**, rules out the alternative constitution **5i**, in which the pyridine C-2′ carbon atom is too far apart from the C-3 methyl protons to undergo any NOE enhancement.

On the other hand, the doubt between constitutions **5g** or **13g** for the product obtained from reaction of **15** with unsubstituted hydrazine could not be solved by NOE methods. However, its constitution was unambiguously determined as **5g** by comparison of its UV spectrum (215 nm, log $\varepsilon$=4.33 and 255 nm, log $\varepsilon$=3.79) with those of **5a** (218 nm, log $\varepsilon$=4.40 and 258 nm, log $\varepsilon$=4.01) and **5g** (218 nm, log $\varepsilon$=4.38 and 259 nm, log $\varepsilon$=3.80).

## Experimental

**General.** Mp's have been determined on a Kofler block (Reichert, Wien). UV spectra were run in a Perkin-Elmer 550 instrument. IR spectra were measured on a Perkin-Elmer 1310 instrument. 80 MHz $^1H$ and 20 MHz $^{13}C$ NMR spectra were recorded in the FT mode on a Bruker WP80SY instrument. MS were taken under EI (70 eV) using a Hewlett-Packard 5985-B instrument.

General preparation procedures, yields and melting points are given in Tables 1—3 and 5. Separations were carried out by column chromatography on silica gel Merck 7754. Special NMR procedures have been described in detail elsewhere: Gaussian resolution enhancement-zero filling,[14] measurement of $^1H\{^1H\}$ NOEs by the NOE difference technique,[15] assignment of carbon spectra by selective proton decoupling[19] and measurement of long range, selective heteronuclear NOE enhancements.[20]

**Dehydroacetic Acid Oxime (2).** Prepared according to the described procedure.[6] IR (KBr) 3400—2500, 1660 $cm^{-1}$; $^1H$ NMR ($d_6$-DMSO) $\delta$=2.15 (3H, s), 2.35 (3H, s), 4.7—6.2 (1H, broad absorption), 6.05 (1H, s); $^{13}C$ NMR ($d_6$-DMSO) $\delta$=13.3, 19.2, 95.1, 102.0, 158.7, 161.9, 163.0, 173.4; MS *m/z* (%) 183 ($M^+$, 44), 166 (33), 139 (21), 126 (38), 85 (36), 69 (33), 67 (35), 43 (100).

**Preparation of Substituted Dehydroacetic Acid Hydrazones 3.** The reaction conditions are summarized in Table 1.

**Dehydroacetic Acid Methylhydrazone (3a).** IR (KBr) 3300, 1690, 1570 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$=2.2 (3H, s), 2.7 (3H, s), 2.8 (3H, s), 5.7 (1H, s); $^{13}C$ NMR ($CDCl_3$) $\delta$=15.9, 19.5, 38.3, 94.8, 106.6, 162.2, 163.6, 172.2, 182.8; MS *m/z* (%) 196 ($M^+$, 35), 181 (18), 154 (22), 139 (100), 111 (25), 85 (38), 69 (40), 43 (82). This compound did not give a correct elemen-

Table 7. The Assigned 20 MHz $^{13}C$ NMR Spectrum of 3,6-Dimethyl-2-(2-pyridyl)pyrano[4,3-*c*]pyrazol-4(2*H*)-one (**13i**) in $CDCl_3$

| Carbon | $\delta_C$/ppm | Selective decoupling[a] | | Selective heteronuclear NOE[b] | |
|---|---|---|---|---|---|
| | | Irradn. at $\delta_H$/ppm | Collapses to a singlet | Presatn. at $\delta_H$/ppm | $\eta$/% |
| $C_3$-Me | 13.5 | 3.1 | Yes | | |
| $C_6$-Me | 19.8 | 2.3 | Yes | | |
| $C_7$ | 96.5 | 6.3 | Yes | | |
| $C_{3a}$ | 106.6 | — | — | 3.1 | +24 |
| $C_{5'}$ | 117.3 | 7.35 | Yes | | |
| $C_{3'}$ | 122.6 | 7.85 | Yes | | |
| $C_{4'}$ | 138.5 | 7.85 | Yes | | |
| $C_3$ | 145.3 | — | — | 3.1 | +66 |
| $C_{6'}$ | 147.7 | 8.50 | Yes | | |
| $C_{7a}$ | 150.6 | 6.3 | Yes | | |
| $C_{2'}$ | 152.5 | — | — | 3.1 | +11 |
| $C_6$ | 157.6 | 2.3 | Yes | | |
| $C_4$ | 159.9 | — | — | 3.1 | +16 |

a) CW irradiation, decoupling power DP=18H (i.e, 18dB attenuation below nominal 10W). b) CW presaturation, decoupling power DP=55L (i.e., $\gamma B_2 \simeq 2.5$ Hz) for 25s.

tal analysis.

**Dehydroacetic Acid Phenylhydrazone (3b).**[12] $^1$H NMR ($d_6$-DMSO): $\delta$=2.05 (3H, s), 2.5 (3H, s), 5.9 (1H, s), 6.8—7.05 (3H, m), 7.1—7.5 (2H, m), 9.05 (1H, s).

**Dehydroacetic Acid (4-Chlorophenyl)hydrazone (3c).** IR (KBr) 3300, 1680, 1590 cm$^{-1}$; $^1$H NMR ($CDCl_3$+$CF_3COOH$) $\delta$=2.4 (3H, s), 3.0 (3H, s), 6.4 (1H, s), 6.8, 6.9, 7.3, 7.4 (4H, AB system); $^{13}$C NMR ($CDCl_3$+$CF_3COOH$) $\delta$=18.3, 19.6, 94.6, 104.4, 115.8, 129.5, 130.1, 141.5, 165.9, 168.8, 175.1, 180.5; MS $m/z$ (%) 294 (20), 292 ($M^+$, 58), 237 (86), 235 (80), 125 (41), 99 (53), 85 (60), 43 (100); Found: C, 57.64; H, 3.99; N, 9.53%. Calcd for $C_{14}H_{13}ClN_2O_3$: C, 57.45; H, 4.48; N, 9.57%.

**Dehydroacetic Acid (4-Nitrophenyl)hydrazone (3d).** IR (KBr) 3180, 1670, 1590 cm$^{-1}$; $^1$H NMR ($CDCl_3$+$CF_3COOH$) $\delta$=2.5 (3H, s), 3.1 (3H, s), 6.4 (1H, s), 7.1, 7.2, 8.4, 8.5 (4H, AB system); $^{13}$C NMR ($CDCl_3$+$CF_3COOH$) $\delta$=17.2, 19.5, 95.7, 105.3, 107.6, 121.8, 142.1, 149.4, 165.5, 166.4, 174.7, 181.8; MS $m/z$ (%) 303 ($M^+$, 86), 261 (42), 246 (100), 85 (61), 43 (80), Found: C, 55.48; H, 4.23; N, 13.73%. Calcd for $C_{14}H_{13}N_3O_5$: C, 55.45; H, 4.32; N, 13.86%.

**Dehydroacetic Acid (2,4-Dinitrophenyl)hydrazone (3e).** IR (KBr) 3300, 1720, 1700, 1570 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$=2.3 (3H, s), 2.7 (3H, s), 6.0 (1H, s), 7.4 (1H, d, $J$=14 Hz), 8.4 (1H, dd, $J$=14 Hz, $J'$=3 Hz), 9.2 (1H, d, $J$=3 Hz), 11.3 (1H, s), 14.7 (1H, s); $^{13}$C NMR ($CDCl_3$+$CF_3COOH$) $\delta$=17.7, 19.4, 96.7, 105.4, 115.0, 121.9, 131.6, 132.4, 140.6, 145.2, 166.8, 168.8, 177.0, 182.3; MS $m/z$ (%) 348 ($M^+$, 36), 306 (20), 291 (28), 256 (26), 151 (43), 109 (44), 85 (54), 67 (90), 43 (100); Found: C, 48.52; H, 3.35; N, 15.93%. Calcd for $C_{14}H_{12}N_4O_7$: C, 48.28; H, 3.47; N, 16.09%.

**Preparation of Pyrano[4,3-*c*]pyrazol-4(1*H*)-ones (5).** The reaction conditions are summarized in Table 2.

**1,3,6-Trimethylpyrano[4,3-*c*]pyrazol-4(1*H*)-one (5a).** UV (EtOH) 218 (log $\varepsilon$=4.40), 258 (log $\varepsilon$=4.01) nm; IR (KBr) 3090, 1720 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$=2.3 (3H, s), 2.5 (3H, s), 3.8 (3H, s), 6.1 (1H, s); $^{13}$C NMR ($CDCl_3$) $\delta$=12.4, 19.9, 35.4, 91.8, 103.4, 145.2, 148.7, 158.6, 159.1; MS $m/z$ (%) 178 ($M^+$, 67), 163 (100), 43 (26); Found: C, 60.67; H, 5.62; N, 15.58%. Calcd for $C_9H_{10}N_2O_2$: C, 60.67; H, 5.66; N, 15.72%.

**3,6-Dimethyl-1-phenylpyrano[4,3-*c*]pyrazol-4(1*H*)-one (5b).**[3b] IR (KBr) 3070, 2950, 1725, 1620, 1590, 1500, 1325, 945, 760 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$=2.2 (3H, s), 2.55 (3H, s), 6.3 (1H, s), 7.3 (5H, s); $^{13}$C NMR ($CDCl_3$) $\delta$=12.6, 20.1, 92.9, 105.0, 123.2, 128.0, 129.5, 138.4, 144.7, 150.2, 158.8, 160.0; MS $m/z$ (%) 240 ($M^+$, 100), 239 (9), 226 (11), 225 (73), 77 (15), 51 (10), 43 (22).

**1-(4-Chlorophenyl)-3,6-dimethylpyrano[4,3-*c*]pyrazol-4-(1*H*)-one (5c).** IR (KBr) 3050, 1740 cm$^{-1}$; $^1$H NMR ($CDCl_3$+$CF_3COOH$) $\delta$=2.4 (3H, s), 2.7 (3H, s), 6.4 (1H, s), 7.4, 7.5, 7.6, 7.7 (4H, AB system); $^{13}$C NMR ($CDCl_3$+$CF_3COOH$) $\delta$=11.4, 19.7, 93.2, 104.9, 126.1, 130.7, 133.6, 137.3, 147.0, 152.0, 161.6, 164.3; MS $m/z$ (%) 276 (34), 274 ($M^+$, 100), 261 (29), 259 (86), 75 (27), 43 (53); Found: C, 60.86; H, 3.88; N, 10.64%. Calcd for $C_{14}H_{11}ClN_2O_2$: C, 61.31; H, 4.01; N, 10.22%.

**1-(4-Hydroxyethyl)-3,6-dimethylpyrano[4,3-*c*]pyrazol-4-(1*H*)-one (5f).** UV (EtOH) 218 (log $\varepsilon$=4.38), 259 (log $\varepsilon$=3.80) nm; IR (KBr) 3360, 1710, 1080, 1030 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$=2.3 (3H, s), 2.5 (3H, s), 3.1 (1H, br), 4.0—4.2 (4H, m), 6.3 (1H, s); $^{13}$C NMR ($CDCl_3$) $\delta$=12.4, 19.9, 51.3, 60.9, 92.5, 103.3, 146.0, 149.2, 159.0, 159.1; MS $m/z$ (%) 209 ($M^+$, 100), 177 (60), 164 (39), 43 (47).

**3,6-Dimethylpyrano[4,3-*c*]pyrazol-4(1*H*)-one (5g).** Prepared following the conditions described in Table 5. UV (EtOH) 215 (log $\varepsilon$=4.33), 255 (log $\varepsilon$=3.79) nm; IR (KBr) 3180, 3120, 1690 cm$^{-1}$; $^1$H NMR ($CDCl_3$+$CF_3COOH$) $\delta$=2.4 (3H, s), 2.9 (3H, s), 6.7 (1H, s); $^{13}$C NMR ($CDCl_3$+$CF_3COOH$) $\delta$=11.2, 20.5, 93.7, 105.1, 147.0, 149.0, 159.3, 165.7; MS $m/z$ (%) 164 ($M^+$, 80), 149 (100), 43 (14); Found: C, 58.26; H, 4.52; N, 17.22%. Calcd for $C_8H_8N_2O_2$: C. 58.53; H, 4.91; N,17.06%.

**Preparation of 5-Hydroxy-3-methyl-4-(3-methyl-1*H*-pyrazol-5-yl)-1*H*-pyrazoles (8).** The reaction conditions are summarized in Table 3.

**1,3-Dimethyl-5-hydroxy-4-(1,3-dimethyl-1*H*-pyrazol-5-yl)-1*H*-pyrazole (8a).** IR (KBr) 2920 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$=2.0 (2H, s), 2.1 (3H, s), 3.5 (3H, s), 3.7 (3H, s), 5.8 (1H, s); $^{13}$C NMR ($CDCl_3$) $\delta$=11.2, 13.0, 30.7, 36.3, 93.6, 106.3, 135.3, 144.2, 147.1, 157.7; MS $m/z$ (%) 206 ($M^+$, 100), 135 (42), 65 (20), 43 (33), Found: C, 58.05; H, 6.96; N, 27.09%. Calcd for $C_{10}H_{14}N_4O$: C, 58.24; H, 6.84; N, 27.16%.

**1-(4-Chlorophenyl)-5-hydroxy-3-methyl-4-[1-(4-chlorophenyl)-3-methyl-1*H*-pyrazol-5-yl]-1*H*-pyrazole (8c).** IR (KBr) 3450, 1610 cm$^{-1}$; $^1$H NMR ($CDCl_3$+$CF_3COOH$) $\delta$=2.3 (3H, s), 2.6 (3H, s), 6.8 (1H, s), 7.2—7.6 (8H); $^{13}$C NMR ($CDCl_3$+$CF_3COOH$) $\delta$=10.6, 93.2, 111.8, 125.8, 126.9, 130.4, 130.5, 131.1, 131.6, 137.6, 139.1, 139.5, 148.2, 149.0, 157.6; MS $m/z$ (%) 402 (12), 400 (62), 398 ($M^+$, 96), 231 (24), 113 (100), 111 (34), 75 (32); Found: C, 60.26; H, 4.04; N, 13.81%. Calcd for $C_{20}H_{16}Cl_2N_4O$: C, 60.30; H, 4.02; N, 14.17%.

**5-Hydroxy-1-(2-hydroxyethyl)-3-methyl-4-[3-methyl-1-(2-hydroxyethyl)-1*H*-pyrazol-5-yl)]-1*H*-pyrazole (8f).** IR (KBr) 3280, 2940 cm$^{-1}$; $^1$H NMR ($D_2O$) $\delta$=2.1 (3H, s), 2.2 (3H, s), 3.8 (4H), 4.0 (4H), 6.1 (1H, s); $^{13}$C NMR ($D_2O$) $\delta$=11.1, 13.2, 47.0, 51.6, 60.2, 61.3, 95.7, 108.0, 136.5, 146.7, 150.0, 161.6; MS $m/z$ (%) 266 ($M^+$, 100), 235 (74), 223 (20), 178 (29); No correct elemental analysis for this compound was achieved.

**3,6-Dimethyl-1-phenylpyrano[2,3-*c*]pyrazol-4(1*H*)-one (9b).**[4] This compound was obtained as by-product in the cyclization reaction of **3b** to **5b**. $^1$H NMR ($CDCl_3$) $\delta$=2.4 (3H, s), 2.6 (3H, s), 6.0 (1H, s), 7.3—7.9 (5H, s); $^{13}$C NMR ($CDCl_3$) $\delta$=13.7, 19.2, 106.7, 112.4, 120.8, 127.1, 129.2, 137.1, 146.5, 153.5, 161.4, 175.4; MS $m/z$ (%) 240 ($M^+$, 100), 200 (70), 132 (20), 91 (58), 77 (15), 51 (10).

**3,6-Dimethylpyrano[4,3-*c*]pyrazol-4(2*H*)-ones (13).** The reaction conditions are summarized in Table 5.

**3,6-Dimethyl-2-phenylpyrano[4,3-*c*]pyrazol-4(2*H*)-one (13b).**[3c,8] IR (KBr) 3070, 2900, 1715, 1635, 1580, 1270, 1220, 1150, 1080, 1040, 960 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$=2.2 (3H, s), 2.6 (3H, s), 6.25 (1H, s), 7.45 (5H, s); $^{13}$C NMR ($CDCl_3$) $\delta$=11.8, 19.9, 96.7, 105.8, 125.3, 129.0, 129.3, 138.6, 143.2, 151.0, 157.4, 160.1; MS $m/z$ (%) 240 ($M^+$, 100), 239 (28), 225 (83), 77 (55), 51 (21), 43 (26).

**2-(4-Chlorophenyl)-3,6-dimethylpyrano[4,3-*c*]pyrazol-4-(2*H*)-one (13c).** IR (KBr) 3100, 1760 cm$^{-1}$; $^1$H NMR ($CDCl_3$+$CF_3COOH$) $\delta$=2.4 (3H, s), 2.7 (3H, s), 6.7 (1H, s), 7.3, 7.4, 7.6, 7.7 (4H, AB system); $^{13}$C NMR ($CDCl_3$+$CF_3COOH$) $\delta$=11.3, 19.6, 95.2, 105.3, 127.4, 130.7, 133.1, 138.5, 147.8, 150.2, 161.6, 163.0; MS $m/z$ (%) 276 (34), 274 ($M^+$, 100), 261 (27), 259 (82), 152 (23), 111 (45), 75 (53), 43 (78); Found: C, 61.21; H, 3.88; N, 10.06%. Calcd for $C_{14}H_{11}ClN_2O_2$: C, 61.31; H, 4.01; N, 10.22.%

**3,6-Dimethyl-2-(4-methylphenyl)pyrano[4,3-*c*]pyrazol-4-(2*H*)-one (13h).** IR (KBr) 3100, 1725 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$=2.3 (3H, d, $J$=1.5 Hz), 2.4 (3H, s), 2.6 (3H, s), 6.3 (1H, q, $J$=1.5 Hz), 7.3 (4H, s); $^{13}$C NMR ($CDCl_3$) $\delta$=11.8, 19.8, 21.0, 96.7, 106.0, 125.1, 129.8, 138.1, 139.1, 143.1, 150.8, 157.2, 160.0; MS $m/z$ (%) 254 ($M^+$, 100), 239 (93), 132 (10), 91

(32); Found: C, 70.58; H, 5.33; N, 10.85%. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H. 5.55; N, 11.02%.

**3,6-Dimethyl-2-(2-pyridyl)pyrano[4,3-*c*]pyrazol-4(2*H*)-one (13i).** IR (KBr) 3080, 1720 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$=2.3 (3H, s), 3.1 (3H, s), 6.3 (1H, s), 7.3 (1H, m), 7.8—7.9 (2H, m), 8.5 (1H, m); $^{13}C$ NMR ($CDCl_3$) $\delta$=13.5, 19.8, 96.5, 106.6, 117.3, 122.6, 138.5, 145.3, 147.7, 150.6, 152.5, 157.6, 159.9; MS *m/z* (%) 241 ($M^+$, 95), 226 (100), 198 (38), 170 (33), 78 (77); Found: C, 64.60; H, 4.29; N, 17.47%. Calcd for $C_{13}H_{11}N_3O_2$: C, 64.72; H, 4.60: N, 17.42%.

**3,6-Dimethyl-2-(3-trifluoromethylphenyl)pyrano[4,3-*c*]-pyrazol-4(2*H*)-one (13j).** IR (KBr) 3100, 1730 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$=2.3 (3H, d, *J*=1.7 Hz), 2.6 (3H, s), 6.3 (1H, q, *J*=1.7 Hz), 7.7 (4H, m); $^{13}C$ NMR ($CDCl_3$) $\delta$=11.8, 19.8, 96.5, 106.2, 122.3 (q, *J*=4 Hz), 124.0 (q, *J*=273 Hz), 125.5 (q, *J*=4 Hz), 128.2, 130.0, 131.7 (q, *J*=33 Hz), 139.0, 143.5, 151.3, 157.8, 159.7; MS *m/z* (%) 308 ($M^+$, 100), 293 (89), 216 (26), 186 (32), 161 (37), 145 (79), 141 (26), 63 (52), 43 (97); Found: C, 58.39; H, 3.48; N, 9.05%. Calcd for $C_{15}H_{11}F_3N_2O_2$: C, 58.45; H, 3.60; N, 9.09%.

**4-Chloro-3-(1-chlorovinyl)-6-methyl-2*H*-pyran-2-one (15).** A solution of **1** (4.02 g, 24 mmol) in 30 ml of phosphoryl chloride was refluxed for 4.5 h. The cooled mixture was poured very slowly and with stirring over 200 g of ice. This water solution was extracted with chloroform and the organic phase was washed with sodium hydrogenocarbonate. This extract was dried over magnesium sulfate and removal of the solvent left 3.6 g of a black residue. This crude was purified by sublimation at 85 °C/0.2 mmHg (1 mmHg=133.322Pa) affording 1.827 g (33% yield) of a white solid identified as **15**: Mp 100 °C (lit: 101 °C (Ref. 9a)); IR (KBr) 3070, 1700 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$=2.2 (3H, s), 5.55 (1H, d, *J*=2 Hz), 5.85 (1H, d, *J*=2 Hz), 6.2 (1H, s); $^{13}C$ NMR ($CDCl_3$) $\delta$=19.6, 106.5, 121.0, 121.2, 130.0, 149.5, 158.9, 162.1; MS *m/z* (%) 208 (5), 206 (32), 204 ($M^+$, 46), 178 (20), 176 (33), 171 (24), 169 (72), 143 (32), 141 (100), 137 (3), 135 (21), 133 (33), 77 (25), 63 (53) ,43 (47); Found: C, 46.65; H, 2.98%. Calcd for $C_8H_6Cl_2O_2$: C, 46.87; H, 2.95%.

Financial support from "Comisión Asesora de Investigación Cientifica y Técnica" through project No. 2014/83 and a generous gift of dehydroacetic acid from LONZA A.G. (Basel) are gratefully acknowledged. We also thank generous funding from "Fundación María Francisca de Roviralta", which allowed the purchase of the NMR spectrometer and "Direcció General d'Ensenyament Universitari", Generalitat de Catalunya, for the NMR data system.

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