# Tetronic Acids and Derivatives. Part V (1). Synthesis of 5-Hydroxy-1*H*-Pyrazoles *via* 4-Hydrazino-5*H*-Furan-2-ones. Reaction of Hydrazines on Tetronic Acids



*Suzanne Gelin* and Patrick Pollet*

Laboratoire de Chimie Organique, Institut National des Sciences Appliquées, 20, Avenue, Albert Einstein, 69621 Villeurbanne-Cedex, France

Received July 17, 1978

The conversion of tetronic acids **1** to 3(1-hydroxyalkyl)-5-hydroxy-1*H*-pyrazole derivatives **3, 5, 7** and **12** is described. The formation is shown to proceed *via* base-catalyzed rearrangement of the intermediate 4-hydrazino-5*H*-furan-2-one derivatives.

*J. Heterocyclic Chem.*, **16**, 505 (1979).

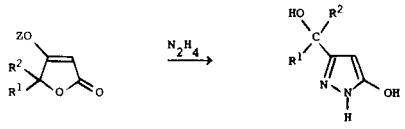
In continuation of our studies on tetronic acids chemistry and on the ring transformations of heterocycles, we examined the action of hydrazines on 3-unsubstituted tetronic acids (4-hydroxy-5*H*-furan-2-ones) **1a-c**. A literature survey only showed the conversion of 4-ethoxy-5*H*-furan-2-one **2a** (Z = $C_2H_5$) to 3-(1-hydroxymethyl)-5-pyrazolone **3a**, along a mechanism described as "normal hydrazinolysis" of the lactone ring (2). The formation of the phenylhydrazone of tetronic acid **1a** with phenylhydrazine has also been described (3); an intermediate pyrazolone is involved to explain the transformation of this phenylhydrazone to photographic dyes (4). 4-Arylhydrazono-3-(1-hydroxyalkyl)-5-pyrazolones have also been prepared by the alkaline rearrangement of osazones of 3,4-dioxo-5*H*-furan-2-ones (5).

Results.

(A) Reaction with Hydrazine.

Reaction of one equivalent of hydrazine hydrate with readily available 4-methoxy-5*H*-furan-2-ones **2a-c** (1) proceeded vigorously to crystalline 5-hydroxypyrazoles **3a-c**. The same products and especially **3a**, identical with Price's compound (2), were more conveniently prepared from tetronic acids **1a-c** and hydrazine hydrate (Scheme I).

SCHEME I



1 Z = H
2 Z = $CH_3$

a, $R^1$=$R^2$=H
b, $R^1$=H, $R^2$=$CH_3$
c, $R^1$=$R^2$=$CH_3$

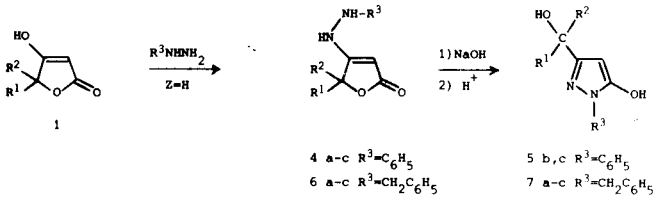
3

Formulation of compounds **3** as 5-hydroxypyrazoles was supported by $^1$H nmr examination (ethylenic proton near 6 ppm without allylic coupling with alkyl chain proton) (6), uv data (7) and the absence of any carbonyl absorption in the ir spectra (8). Similar predominance of this enolic form has been recently demonstrated in solid state or in polar solvents (9) by $^{13}$C nmr with related 3-(1-phenoxyalkyl)-5-hydroxy-1*H*-pyrazoles (10).

(B) Reaction with Phenylhydrazine and Benzylhydrazine.

This facile preparation cannot be directly generalized to *N*-substituted 5-hydroxypyrazoles. Phenyl and benzyl hydrazines reacted smoothly with tetronic acids **1a-c** to give the 4-(2-*N*-substituted hydrazino)-5*H*-furan-2-ones **4** and **6**. The hydrazino structure (with endocyclic double bond) of these compounds was clearly demonstrated by the ir and nmr data (Table 1). In contrast, phenylhydrazine and benzylhydrazine do not react with methyl tetronates **2** under the same conditions. However, it was found that the compounds **4** and **6** were readily dissolved in 50% ethanolic sodium hydroxide solution and afforded upon acidification, the expected *N*-phenyl or *N*-benzyl-3-(1-hydroxyalkyl)-5-hydroxypyrazoles **5b,c** or **7a-c**. In the case of **4a**, the reaction afforded a dark vitrous material in which the pyrazole **5a** could not be detected (Scheme II).

SCHEME II



1

4 a-c $R^3$=$C_6H_5$
6 a-c $R^3$=$CH_2C_6H_5$

5 b,c $R^3$=$C_6H_5$
7 a-c $R^3$=$CH_2C_6H_5$

The 5-hydroxypyrazole structure of compounds **5** and **7** was supported by mechanistic considerations (Discussion) and by spectral data which are neatly inconsistent with a possible (although less probable) 3-hydroxypyrazole formulation. For example, compounds **5** ($R^3$ = $C_6H_5$) displayed an uv absorption at 247 nm in full agreement with the known data of the 1-*N*-aryl-5-pyrazolones (246 nm against 257 nm for the isomeric 1-*N*-aryl-3-pyrazolones) (11a). On the other hand, compounds **5** and **7** showed in the ir spectra a strong carbonyl absorption at 1700 $cm^{-1}$ in chloroform solution which faded in solid state (nujol or

*0022-152X/79/030505-04$02.25*

Table 1

Physical and Analytical Data for 3(1-Hydroxyalkyl)-5-hydroxypyrazoles

| Compound No. | Yield % (a) | M.p. °C (b) | Formula | Analyses % Calcd./Found C | H | N | Uv in Ethanol λ max nm (ε) | Nmr (Ppm) (Perdeuteriopyridine) |
|---|---|---|---|---|---|---|---|---|
| **3a** | 61 (88) | 156 (c) (ethanol) | $C_4H_6N_2O_2$ | | | | 223 (3364) | 4.98 (s, 2H), 6.05 (s, 1H), 9.88 (m, 3H) |
| **3b** | 71 (77) | 163 (ethanol) | $C_5H_8N_2O_2$ | 46.87 47.10 | 6.29 6.51 | 21.87 21.66 | 224 (3646) | 1.73 (d, 3H, J = 7), 5.28 (q, 1H, J = 7), 6.0 (s, 1H), 9.5 (m, 3H) |
| **3c** | 57 (79) | 184 (ethanol) | $C_6H_{10}N_2O_2$ | 50.69 50.83 | 7.09 7.15 | 19.71 19.71 | 223 (3833) | 1.79 (s, 6H), 5.99 (s, 1H), 8.58 (m, 3H) |
| **5b** | 69 | 103 (acetonitrile) | $C_{11}H_{12}N_2O_2$ | 64.69 64.46 | 5.92 5.80 | 13.72 13.60 | 247 (15287) | 1.76 (d, 3H, J = 7), 5.35 (q, 1H, J = 7), 6.0 (m, 1H), 7.2-7.6 (m, 3H), 8.3 (m, 2H), 9.9 (m, 2H) |
| **5c** | 84 | 128 (acetonitrile) | $C_{12}H_{14}N_2O_2$ | 66.03 66.00 | 6.47 6.39 | 12.84 12.69 | 247 (18374) | 1.93 (s, 6H), 6.05 (m, 1H), 7.2-7.6 (m, 3H), 8.3 (m, 2H), 9.58 (m, 2H) |
| **7a** | 81 | 179 (acetonitrile) | $C_{11}H_{12}N_2O_2$ | 64.69 64.61 | 5.92 6.03 | 13.72 13.62 | 247 (5188) | 4.87 (s, 2H), 5.52 (s, 2H), 6.12 (s, 1H), 7.4-7.5 (m, 7H) |
| **7b** | 73 | 149 (acetonitrile) | $C_{12}H_{14}N_2O_2$ | 66.03 66.02 | 6.47 6.54 | 12.84 12.80 | 254 (4937) | 1.77 (d, 3H, J = 7), 5.3 (q, 1H, J = 7), 5.35 (s, 2H), 5.95 (s, 1H), 7.4-7.5 (m, 7H) |
| **7c** | 84 | 141 (ethanol) | $C_{13}H_{16}N_2O_2$ | 67.21 67.21 | 6.94 6.83 | 12.06 11.91 | 254 (5083) | 1.83 (s, 6H), 5.4 (s, 2H), 5.95 (s, 1H), 7.1-7.5 (m, 7H) |
| **12c** | 61 | 151 | $C_7H_{12}N_2O_2$ | 53.83 53.51 | 7.74 7.75 | 17.94 17.93 | 248 (5247) | 1.80 (s, 6H), 3.7 (s, 3H), 5.87 (s, 1H), 7.2 (s, 2H) |

(a) Yields between parentheses are referred to procedure B (from compounds **2**). (b) Crystallisation solvent. (c) Lit. (2) m.p. 156°.

Table 2

Physical and Analytical Data for 4-(Alkylhydrazino)-5*H*-furan-2-ones

| Compound No. | Yield % (a) | M.p. °C (b) | Formula | Analyses % Calcd./Found C | H | N | Uv in Ethanol λ max nm (ε) | Nmr (Ppm) (Perdeuteriopyridine) |
|---|---|---|---|---|---|---|---|---|
| **4a** | 87 | 128 (c) (ethanol) | | | | | 257 (23,095) | 5.15 (s, 2H), 5.25 (s, 1H), 7.2 (m, 5H), 8.95 (s, 1H), 10.58 (s, 1H) |
| **4b** | 93 | 158 (ethanol) | $C_{11}H_{12}N_2O_2$ | 64.69 64.48 | 5.92 5.86 | 13.72 13.69 | 256 (19,193) | 1.6 (d, 3H, J = 7), 5.7 (s, 1H), 5.73 (q, 1H, J = 7), 7.2 (m, 5H), 8.91 (s, 1H), 10.4 (s, 1H) |
| **4c** | 98 | 194 (ethanol) | $C_{12}H_{14}N_2O_2$ | 66.03 66.12 | 6.47 6.51 | 12.84 12.79 | 256 (21,124) | 1.68 (s, 6H), 5.2 (s, 1H), 7.2 (m, 5H), 8.93 (s, 1H), 10.36 (s, 1H) |
| **6a** | 89 | 123 (acetonitrile) | $C_{11}H_{12}N_2O_2$ | 64.69 64.54 | 5.92 5.81 | 13.72 13.78 | 260 (23,322) | 4.18 (s, 2H), 4.83 (s, 2H), 5.2 (s, 1H), 5.75 (s, 1H), 7.2-7.5 (m, 5H), 9.73 (s, 1H) |
| **6b** | 87 | 132 (ethanol) | $C_{12}H_{14}N_2O_2$ | 66.03 66.07 | 6.47 6.42 | 12.84 12.81 | 258 (20,510) | 1.45 (d, 3H, J = 7), 4.17 (s, 2H), 5.0 (q, 1H, J = 7), 5.3 (m, 2H), 7.2-7.5 (m, 5H), 9.5 (m, 1H) |
| **6c** | 93 | 136 (ethanol) | $C_{13}H_{16}N_2O_2$ | 67.22 67.36 | 6.94 6.88 | 12.06 11.90 | 259 (21,812) | 1.55 (s, 6H), 4.17 (s, 2H), 5.3 (m, 2H), 7.2-7.5 (m, 5H), 941 (m, 1H) |
| **8a** | 85 (77) | 147 (ethanol) | $C_5H_8N_2O_2$ | 46.67 46.53 | 6.29 6.27 | 21.87 21.63 | 264 (22,939) | 3.06 (s, 3H), 4.83 (t, 1H, J = 1), 5.0 (d, 2H, J = 1), 5.16 (m, 2H) |
| **8b** | 78 (85) | 151 (ethanol) | $C_6H_{10}N_2O_2$ | 50.69 50.42 | 7.09 7.00 | 19.91 19.99 | 263 (24,186) | 1.57 (d, 3H, J = 7), 3.0 (s, 3H), 4.68 (s, 1H), 4.82 (m, 2H), 5.18 (q, 1H, J = 7) |
| **8c** | 42 | 120 (ethanol) | $C_7H_{12}N_2O_2$ | 53.83 53.68 | 7.74 7.49 | 17.94 18.00 | 263 (23,741) | 1.76 (s, 6H), 3.1 (s, 3H), 4.68 (s, 1H), 5.3 (s, 2H) |
| **9c** | 31 | 139 (acetonitrile) | $C_7H_{12}N_2O_2$ | 53.83 54.01 | 7.74 7.70 | 17.94 17.91 | 256 (22,286) | 1.6 (s, 6H), 2.76 (s, 3H), 5.2 (s, 1H), amino protons unobserved |

(a) Yields between parentheses are referred to procedure B (from compunds **2**). (b) Crystallization solvent. (c) Lit. M.p. 128° (3).

potassium bromide). The presence of this carbonyl band is only consistent with a 5-pyrazolone structure since isomeric 3-pyrazolone displayed no absorption in such a solvent (11b). The position of the phenyl group in the 5-hydroxy-1-phenylpyrazoles is also indicated by the splitting pattern of the aryl protons. The two *ortho* protons are deshielded by about 1 ppm, compared with *meta* and *para* protons. A literature survey only showed these multiplet

patterns in 2-unsubstituted-5-hydroxy-1-phenylpyrazole derivatives where the phenyl and pyrazole rings can be coplanar (11c,16).

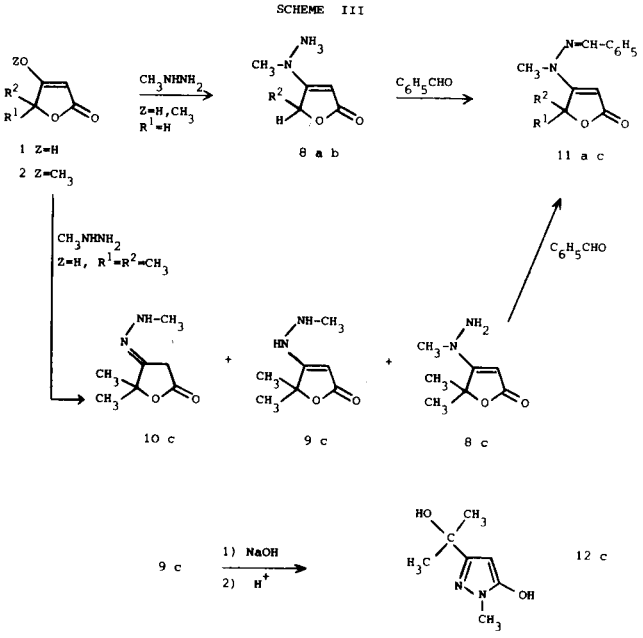
(C) Reaction with Methylhydrazine

In contrast with the two previously studied mono-substituted hydrazines, methylhydrazine reacted with both tetronic acids **1a,b** and methyl tetronates **2a,b** to give 4-(1-*N*-methylhydrazino)-5*H*-furan-2-ones **8a,b**. The structure of compounds **8** was deduced from $^1$H nmr data ($\delta$ = 3 ppm for the methyl group in -N($CH_3$)$NH_2$) (12) and by the conversion into Schiff's base (*eg.*, **11a**) using benzaldehyde. From 5,5-dimethyltetronic acid **1c**, this reaction afforded a mixture of the two possible *N*-hydrazino compounds **8c** and **9c** and a minor amount of hydrazone **10c** (13). The relative ratio of these isomers was found dependent of the reaction solvent:

| Solvent | % **8c** | % **9c** | % **10c** |
|---|---|---|---|
| Ethanol | 35 | 41 | 24 |
| Acetonitrile | 45 | 42 | 13 |
| Methylene chloride | 55 | 45 | 0 |

In contrast, the methyl 5,5-dimethyl tetronate **2c** was recovered unaffected, even after a lengthened reaction time. Compounds **8c** and **9c** were readily separated by fractional crystalliztion and their structures were fully determined by $^1$H nmr: $\delta$ = 3 ppm for $NCH_3$ protons in **8c** and 2.76 ppm for $NHCH_3$ in **9c** (12) and by the formation of a Schiff's base **11c** from **8c**. Only compound **9c** was founded convertible to *N*-methyl-5-hydroxypyrazole **12c** in sodium hydroxide, whilst the compounds **8a-c** were found to be resistant to any ring cleavage with sodium hydroxide, sodium ethoxide or hydrazine (14) (Scheme III).

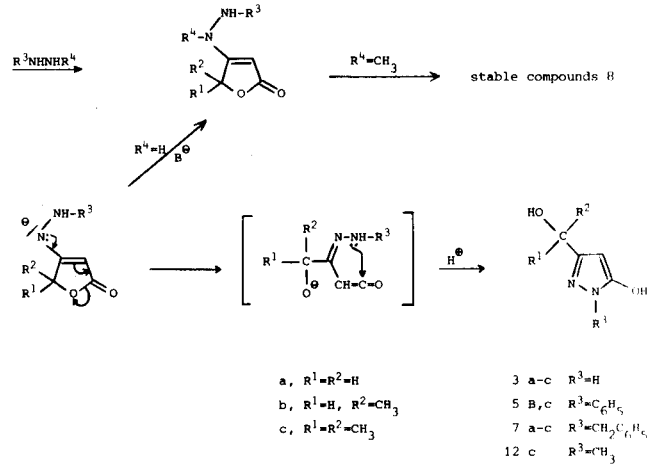
SCHEME III



Discussion.

The formation of compounds **5**, **7** and **12c** is easily rationalized by postulating a proton abstraction with base from the 1-amino group of the enehydrazines leading to an anionic intermediate, owing to the possibility of further delocalisation of the negative charge, the anion undergoing the rearrangement (15) (Scheme IV).

SCHEME IV



The best evidence for this mechanistic pathway it that the 1-*N*-substituted compounds **8** cannot be rearranged either by hydrazine or by hydroxide ion. The lacton ring of tetronic system then showed a great stability to cleavage. Furthermore, the fact that similr products are formed from the tetronic acids *1* (p*K*a 3.76 for **1a**) (16) and from the methyl tetronates **2** with hydrazine or methylhydrazine (if it works) indicates that the first step of all above reactions leads to 4-hydrazinofuranone derivatives by hydrazine salts formation and dehydration (from **1**) or by conjugate addition-elimination (from **2**). In the case of compounds **3**, the suggestion of a "normal hydrazinolysis" (2) of the carbonyl lactone was then rendered inconsistent. Although the hydrazino derivatives were not isolated or detected, our results seem to indicate that such intermediate are generated; the hydrazine, a stronger base than the phenyl or benzylhydrazines, itself promotes the base-catalyzed opening followed by internal cyclization as above, leading to 5-hydroxypyrazoles **3**.

In summary, the reaction of readily accessible tetronic acids and hydrazines, through intermediate 4-hydrazino-5*H*-furan-2-ones, affords a convenient means for the synthesis of 3-(1-hydroxyalkyl)-5-hydroxy-*N*-unsubstituted or substituted pyrazoles.

## EXPERIMENTAL

All melting points were taken on a Reichert hot plate aparatus and are uncorrected. Infrared spectra are obtained with a Beckmann model Ac-

culab 2 spectrophotometer. $^1$H nmr spectra were taken on a Varian A 60. The chemical shifts reported are in parts per million from internal TMS. Microanalyses were performed by Microanalytical Laboratory, Centre National de la Recherche Scientifique, Villeurbanne, France.

Compounds **1** and **2** were prepared as previously described (1).

General Method of Preparation of the 3-(1-Hydroxyalkyl)-5-hydroxy-1*H*-pyrazoles (**3**).

A solution of tetronic acid **1a-c** (10 mmoles, procedure A), or of methyl tetronate **2a-c** (10 mmoles, procedure B), and hydrazine hydrate (0.5 g., 10 mmoles) in absolute ethanol (10 ml.) was heated on a steam bath for half an hour. Concentration *in vacuo* afforded an oily material which was crystallized by trituration with chloroform (10 ml.) and recrystallized once from ethanol to pure title compounds (Table 1).

General Method of Preparation of the 4-(2-*N*-Phenylhydrazino)- or 4-(2-*N*-Benzylhydrazino)-5*H*-furan-2-ones (**4** and **6**).

A solution of tetronic acid **2a-c** (10 moles) and phenylhydrazine or benzylhydrazine 10 mmoles, (1.08 g. and 1.22 g., respectively) in ethanol (5 ml.) was heated on a steam bath for one hour. On cooling and occasionnal scratching, the solution deposited white needles of nearly pure title compounds which was recrystallized once from ethanol (Table 2).

4-(1-*N*-Methylhydrazino)-5*H*-furan-2-ones (**8a,b**).

A solution of tetronic acid **1a,b** (10 mmoles, procedure A) or of methyl tetronate **2a,b** (10 mmoles, procedure B) and methylhydrazine (0.55 ml., 10 mmoles) in ethanol (10 ml.) was heated on a steam bath for one hour. Upon concentration *in vacuo*, the oily residual material crystallized. Compounds **8a,b** were recrystallized from ethanol (Table 2).

Reaction of **1c** with Methylhydrazine.

4-(1-*N*-Methylhydrazino-5,5-dimethyl-5*H*-furan-2-one (**8c**) and 4-(2-*N*-Methylhydrazino)-5,5-dimethyl-5*H*-furan-2-one (**9c**).

A solution of 5,5-dimethyl tetronic acid **2c** (1.28 g., 10 mmoles) and methylhydrazine (0.55 ml., 10 mmoles), in dichloromethane (10 ml.) was treated as above. The semi-crystalline residual material was examined by $^1$H-nmr and proved to be a mixture of **8c** and **9c**. This residue was dissolved in boiling acetonitrile (4 ml.). On cooling and scratching the solution in an ice bath, it deposited 480 mg. (31%) of nearly pure compound which was recrystallized once from acetonitrile and characterized as **9c** (Table 2). The filtrate was concentrated *in vacuo*, crystallized by scratching and cooling on ice and recrystallized from ethanol (3 ml.) to **8c**. Recrystallization from ethanol leads to pure material, 655 mg. (42%) (Table 2).

4-(2-*N*-Benzylidene-1-*N*-methylhydrazino)-5*H*-furan-2-ones (**11a,c**).

Compound **8a,c** (2 mmoles) and benzaldehyde (212 mg., 2 mmoles), in ethanol (5 ml.) was heated for few minutes in a test tube. On cooling and scratching, the solution deposited white plates of compound **11** which was purified by vacuum sublimation.

Compound **11a**.

This compound was obtained in a yield of 93%, m.p. 233-234° dec.; nmr (DMSO-$d_6$): 3.45 (s, 3H), 5.2 (s, 2H), 5.3 (s, 1H), 7.5-7.8 (m, 5H), 8.1 ppm (s, 1H).

*Anal.* Calcd. for $C_{12}H_{12}O_2N_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.54, H, 5.60; N, 12.92.

Compound **11c**.

This compound was obtained in a yield of 87%, m.p. 150°; nmr (DMSO-$d_6$): 1.8 (s, 6H), 3.21 (s, 3H), 5.2 (s, 1H), 7.3-7.7 (m, 5H), 7.8 ppm (s, 1H).

*Anal.* Calcd. for $C_{14}H_{16}O_2N_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.71; H, 6.32; N, 11.50.

General Method of Preparation of the 3-(1-Hydroxyalkyl)-5-hydroxy-1*H*-Pyrazoles **5,7** and **12**).

To a refluxing solution of compounds **4,6** or **9** (10 mmoles) in ethanol (10 ml.) 1*N* sodium hydroxide (12 ml.) was added and the solution was heated on a steam bath for half an hour. During this time, the solution turned from deep green to pale red with compounds **4** but remained pale yellow from compounds **6** and **9** (14). After evaporation of the ethanol *in vacuo*, the solution was washed twice with ethyl acetate, acidified with glacial acetic acid (0.8 ml.) and exhaustively extracted with ethyl acetate (10 X 20 ml.). Drying over anhydrous sodium sulfate, concentration *in vacuo* and further elimination of acetic acid by azeotropic distillation with benzene (30 ml.) afforded colored oils which readily crystallized. Recrystallization from acetonitrile leads to pure title compounds (Table 1).

## REFERENCES AND NOTES

(1) P. Pollet and S. Gelin, *Tetrahedron*, **34**, 1453 (1978).

(2) J. F. Gillespie and C. C. Price, *J. Org. Chem.*, **22**, 780 (1957); T. Okuda and C. C. Price, *ibid.*, **23**, 647 (1958).

(3) L. Wolff, *Ann. Chem.*, **291**, 235 (1896).

(4) G. Duffin and J. D. Kendall, British Patent 828 847 (20 Feb. 1960); *Chem. Abstr.*, **54**, P15036 (1960).

(5) G. Duffin and J. D. Kendall, *J. Chem. Soc.*, 3369 (1955); H. Ohle and G. Böckmann, *Ber.*, **67**, 1751, 1762 (1934); S. H. El Ashry, Y. E. Kilany and F. Singab, *Carbohyd. Res.*, **56**, 93 (1977); S. H. El Ashry, H. Nasser and F. Singab, *ibid.*, **56**, 200 (1977); H. M. Mokhtar, Z. M. El-Shafei, H. S. El Khadem and D. L. Swartz, *J. Heterocyclic Chem.*, **14**, 927 (1977) and references cited therin.

(6) A. R. Katritzky and F. W. Maine, *Tetrahedron*, **20**, 299, 315 (1964); G. A. Newman and P. J. S. Pauwels, *ibid.*, **25**, 4605 (1969).

(7) H. Dorn, *J. Prakt. Chem.*, **315**, 382 (1973).

(8) C. Sabate-Alduy and J. Lematre, *Bull. Soc. Chim. France*, 4189 (1969).

(9) Our compounds are only soluble in polar solvents such as DMSO, pyridine alcohols and water.

(10) G. Auzou, R. Rips and J. Likforman, *Tetrahedron Letters*, 2245 (1976).

(11) J. Elguero, R. Jacquier and G. Tarrago, *Bull. Soc. Chim. France*, 3789 (1967); *ibid.*, 3783 (1967); *ibid.*, 3777 (1967).

(12) W. Sucrow and E. Wiese, *Chem. Ber.*, **103**, 1767 (1970); W. Sucrow and E. Wiese, *ibid.*, **109**, 261 (1976).

(13) Attempted isolation of compound **10c** failed; its structure was only tentatively assigned by $^1$H nmr data of the crude reaction product (perdeuteriopyridine): 1.65 (s, 6H), 3.08 (s, 3H), 3.63 (s, 2H).

(14) Accordingly, when a crude mixture of compounds **8c, 9c, 10c** was treated with 1*N* sodium hydroxide, pure compound **8c** was recovered by ethyl acetate washing of the alkaline solution and the *N*-methyl-5-hydroxypyrazole **12c** was then obtained after acidifiction and extraction; overall yield from **2c**, 27%.

(15) Cyclization of phenylhydrazone of diketene to 1-phenyl-3-methyl-5-pyrazolone is known. See H. Z. Lecher, R. P. Parker and R. C. Conn, *J. Am. Chem. Soc.*, **66**, 1959 (1944).

(16) T. J. Batterman "Nmr Spectra of simple Heterocycles", Wiley Intersciences, New York, N. Y., 1973 pp. 190-200.