# Methylation and Proton Magnetic Resonance Spectra of Some Pyrazolo[3,4-*d*- and 4,3-*d*]pyrimidinediones (1)

*C. S. Mahajanshetti (2) and Ludwig Bauer**

Department of Medicinal Chemistry, College of Pharmacy,
University of Illinois at the Medical Center, Chicago, Illinois 60680

Received August 19, 1974

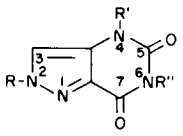
Some time ago, we synthesized a number of isomeric *N*-1 and *N*-2 methyl and phenyl *N*-hydroxypyrazoloauracils I-IV, (R = $CH_3$ or $C_6H_5$, R′ = H, R″ = OH) whose structures were established by a combination of chemical and spectral analyses (3,4). Attempts to alkylate the NOH or NH groups in these systems preferentially resulted in a series of *O*,*N*-dialkyl derivatives. Methylation of these *N*-hydroxypyrazolouracils furnished a series of derivatives represented by Ia-IVa (R = $CH_3$) and Ib-IVb (R = $C_6H_5$). To aid the chemical shift assignment of various methyl groups, the methyl resonances of the *N*,*N*′,*N*″-trimethyl derivatives, Ic-IVc, were also included as well as those for IVd. Pertinent chemical shifts are assembled in Table I.

Pyrazole Proton Resonances.

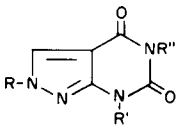
Essentially, chemical shifts differences were utilized to distinguish between pairs of isomers as I and II, III and IV. The vicinal C=O group at C-4 in II and IV shielded the H-3 pyrazole protons considerably causing these to resonate further downfield than H-3 in isomers I and III.

Methyl Resonances.

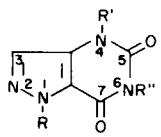
The magnetic environment for these various methyl protons was sufficiently different to distinguish between



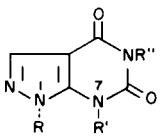
I



II



III



IV

a, R = R′ = $CH_3$, R″ = $OCH_3$
b, R = $C_6H_5$, R′ = $CH_3$, R″ = $OCH_3$
c, R = R′ = R″ = $CH_3$
d, R = R″ = $CH_3$, R′ = H

*O*- and *N*-$CH_3$ groups. The pyrazole *N*-$CH_3$ resonances are discussed first. In Ia-IVa and Ic-IVc, these appeared as singlets over a narrow range, δ 3.91-4.09. As might be expected, the influence of the neighboring C=O group in IIIa and IIIc caused the 1-methyl protons to be most deshielded and thus gave rise to pmr signals furthest downfield in this series (5). These shifts are analogous to those for N-7 and N-9 methyl groups in xanthines and caffeines which were observed as singlets around δ 4.00 (6-10). As expected, the *O*-$CH_3$ pmr signals in Ia-IVa and Ib-IV appeared consistently between δ 3.82-3.89, considerably further downfield from the *N*-$CH_3$ resonances in the uracil ring. Thus having assigned the pyrazole *N*-methyl and the uracil *O*-methyl signals, the remaining signals between δ 3.32 and 3.67 must be due the remaining *N*-methyl group on the uracil ring of Ia-IVa. Compound IVd (12) helped to corroborate this assignment. It appeared that in one of these isomers, *viz.*, IVa, the N-7 methyl protons were downfield by some 0.3 ppm. In the corresponding trimethyl series, Ic-IVc, (13), again IVc showed that the N-7 methyl protons were more deshielded than comparable *N*-methyl protons in the other three isomers, Ic-IIIc. This shift was attributed to a peri-interaction of the two methyl groups on N-1 and N-7 in IVa or IVc, possibly due to an anisotropic effect of the N-1 methyl group on the N-7 methyl protons. A similar effect has been reported for the downfield shift of the N-9 methyl protons of 1,3,9-trimethylxanthine compared to those of 1,3,7-trimethylxanthine. The 9-$CH_3$ protons were deshielded by some 0.17 ppm (7-9).

A different phenomenon was noted for one of the chemical shifts of one of the methyl signals of Ib-IVb. The N-7 methyl signal in IVb was shielded and moved upfield by some 0.4 ppm compared to the methyl resonances in Ib-IIIb. These data suggest that the anisotropy of the phenyl ring on N-1 in IVb exerts a shielding effect on these neighboring methyl protons on N-7. A sizeable upfield shift of alkyl proton resonances is noted when the protons lie above the plane of the aromatic ring and one might conclude that the phenyl group on N-1 does not lie in the plane of the heteroaromatic ring system but at a considerable angle. This premise is reasonable in terms of

Table I

Chemical shifts [δ, downfield from TMS] in DMSO-$d_6$ (a)

| Compound | Pyrazole Proton H-3 | R | R′ | R″ |
|---|---|---|---|---|
| Ia | 8.00 | 4.01 | 3.32 | 3.86 |
| IIa | 8.38 | 3.91 | 3.37 | 3.85 |
| IIIa | 7.71 | 4.08 | 3.38 | 3.85 |
| IVa | 7.87 | 4.08 | 3.67 | 3.82 |
| Ib | 8.70 | 8.05-7.35 | 3.43 | 3.89 |
| IIb | 9.28 | 8.12-7.33 | 3.47 | 3.87 |
| IIIb | 7.90 | 7.78-7.40 | 3.46 | 3.89 |
| IVb | 8.15 | 7.56 | 3.06 | 3.89 |
| Ic | 7.99 | 4.01 | 3.33 | 3.25 |
| IIc | 8.38 | 3.91 | 3.37 | 3.22 |
| IIIc | 7.70 | 4.09 | 3.35 | 3.22 |
| IVc | 7.88 | 4.06 | 3.67 | 3.25 |
| IVd | 7.85 | 3.81 | - | 3.26 |

(a) All signals were singlets, except those for the phenyl proton resonances of Ib, IIb and IIIb, which were complex multiplets over the range so indicated.

steric interactions of these two neighboring groups at N-1 and N-7 in IVb. Similar shifts have been reported for a series of 1-phenyl-7-methylindazoles (14). The C-7 methyl resonances in that system were found considerably further upfield to those of other aromatic C-methyl groups in that system (~ 0.6 ppm) which could be explained if similar geometry and anisotropic effects operate in that and our system.

## EXPERIMENTAL

Melting points were determined on a Mel-Temp apparatus in capillary tubes and are not corrected. Analyses were performed by Micro-Tech Laboratories, Inc., Skokie, Illinois. The pmr spectra were determined from Varian A-60 spectrometer and chemical shifts recorded as ppm (δ) downfield from TMS as the internal standard. Uv spectra were determined on Beckman DK-1 spectrometer in 95% ethanol.

1-Methyl-5-benzyloxy-7-benzylpyrazolo(3,4-*d*)pyrimidine-4,6(5*H*,7*H*)dione (IV, R = $CH_3$, R′ = $CH_2C_6H_5$, R″ = $OCH_2C_6H_5$).

Freshly distilled benzyl chloride (0.7 g.) was added to a mixture of IV (where R = $CH_3$, R′ = H, R″ = OH; 0.2 g.) and anhydrous potassium carbonate (1 g.) in acetone (25 ml.). The mixture was refluxed for 12 hours and worked up as described in the general procedure provided for below. The product (0.18 g., 45%) was recrystallized from methanol-benzene (1:1), m.p. 164-165°; pmr (deuteriochloroform): showed singlets at δ 7.94 (pyrazole proton), 7.43, 7.34 (two phenyl groups), 5.43, 5.11 ($CH_2$'s) and 3.90 (N-$CH_3$).

*Anal.* Calcd. for $C_{20}H_{18}N_4O_3$: C, 66.30; H, 4.97; N, 15.47. Found: C, 66.36; H, 5.04; N, 15.40.

1-Methyl-4-benzyl-6-benzyloxypyrazolo(4,3-*d*)pyrimidine-5,7(4*H*,6*H*)dione (III, R = $CH_3$, R′ = $CH_2C_6H_5$; R″ = $OCH_2C_6H_5$).

By a similar method, III (R = $CH_3$, R′ = H, R″ = OH) was converted in 43% yield as described above, m.p. 172-173°.

*Anal.* Calcd. for $C_{20}H_{18}N_4O_3$: C, 66.30; H, 4.97; N, 15.47. Found: C, 66.28; H, 4.81; N, 15.55.

General Procedure for the Methylation of *N*-Substituted Pyrazolo-*N*-hydroxyuracils.

To a stirred suspension of powdered anhydrous potassium carbonate (2 g., 0.015 mole) in pure acetone (50 ml.) was added 0.003 mole of a finely powdered pyrazolo-*N*-hydroxyuracil, I-IV (R = $CH_3$ or $C_6H_5$, R′ = H and R″ = OH), and then methyl iodide (1 ml.). The mixture was heated on a steam bath for 2 hours. Two lots of methyl iodide (1 ml.) and (0.5 ml.) were further added at 4 hour intervals and heating continued for a total of 12 hours. After cooling, precipitates were filtered off and the residue washed with acetone. The combined filtrates were concentrated to about 2 ml. *in vacuo*. A few drops of water were added to the concentrate to dissolve traces of potassium carbonate and the mixture permitted to stand until the methylated product had separated. It was filtered off, washed with cold water and crystallized from ethanol. Various products are described below.

2,4-Dimethyl-6-methoxy-2*H*-pyrazolo(4,3-*d*)pyrimidine-5,7(4*H*,6*H*)dione (Ia).

Needles, m.p. 243-245°, (58%); uv: max 288 nm (log ε 3.69).

*Anal.* Calcd. for $C_8H_{10}N_4O_3$: C, 45.72; H, 4.76; N, 26.67. Found: C, 45.80; H, 4.95; N, 26.76.

2,7-Dimethyl-5-methoxy-2*H*-pyrazolo(3,4-*d*)pyrimidine-4,6-(5*H*,7*H*)dione (IIa).

Plates, m.p. 224-225°, (60%); uv: max 240 (log ε 3.74) and 262 nm (log ε 3.88).

*Anal.* Calcd. for $C_8H_{10}N_4O_3$: C, 45.72; H, 4.76; N, 26.67. Found: C, 45.89; H, 4.82; N, 26.68.

1,4-Dimethyl-6-methoxy-1*H*-pyrazolo(4,3-*d*)pyrimidine-5,7(4*H*,6*H*)dione (IIIa).

M.p. 210-212°, (59%); uv: max 291 nm (log ε 3.75).

*Anal.* Calcd. for $C_8H_{10}N_4O_3$: C, 45.72; H, 4.76; N, 26.67. Found: C, 45.81; H, 4.71; N, 26.80.

1,7-Dimethyl-5-methoxy-1*H*-pyrazolo(3,4-*d*)pyrimidine-4,6-(5*H*,7*H*)dione (IV).

M.p. 210-211°, (61%); uv: max 239 (log ε 3.82) and 253 nm (log ε 3.81).

*Anal.* Calcd. for $C_8H_{10}N_4O_3$: C, 45.72; H, 4.76; N, 26.67. Found: C, 45.82; H, 4.75; N, 26.75.

2-Phenyl-4-methyl-6-methoxy-2*H*-pyrazolo(4,3-*d*)pyrimidine-5,7-(4*H*, 6*H*)dione (Ic).

M.p. 241-243°, yield (64%); uv: max 302 nm (log ε 4.10).

*Anal.* Calcd. for $C_{13}H_{12}N_4O_3$: C, 57.35; H, 4.41; N, 20.59. Found: C, 57.60; H, 4.44; N, 20.44.

2-Phenyl-5-methoxy-7-methyl-2*H*-pyrazolo(3,4-*d*)pyrimidine-4,6-(5*H*, 7*H*)dione (IIc).

M.p. 259-262°, (62%); uv: max 293 nm (log ε 4.19).

*Anal.* Calcd. for $C_{13}H_{12}N_4O_3$: C, 57.35; H, 4.41; N, 20.59. Found: C, 57.77; H, 4.09; N, 20.63.

1-Phenyl-4-methyl-6-methoxy-1*H*-pyrazolo(4,3-*d*)pyrimidine-5,7-(4*H*, 7*H*)dione (IIIc).

M.p. 248-249°, (60%); uv: max 296 nm (log ε 3.96).

*Anal.* Calcd. for $C_{13}H_{12}N_4O_3$: C, 57.35; H, 4.41; N, 20.59. Found: C, 57.52; H, 4.38; N, 20.53.

1-Phenyl-5-methoxy-7-methyl-1*H*-pyrazolo(3,4-*d*)pyrimidine-4,6-(5*H*, 7*H*)dione (IVc).

M.p. 262-263°, yield 52%; uv: max 231 nm (log $\epsilon$ 4.12).

*Anal.* Calcd. for $C_{13}H_{12}N_4O_3$: C, 57.35; H, 4.41; N, 20.59. Found: C, 57.41; H, 4.54; N, 20.67.

1,5-Dimethyl-1*H*-pyrazolo(3,4-*d*)pyrimidine-4,6(5*H*, 7*H*)dione (IVd).

Granules, m.p. 288-290°, lit. m.p. 297-298°; uv: max 235 nm (log $\epsilon$ 3.70). This compound was prepared according to the literature method (13).

## REFERENCES

(1) Presented on January 14, 1974 at the 5th International Symposium on Magnetic Resonance, Bombay, India.

(2) Present address: Department of Chemistry, Karnatak University, Dharwar, Karnataka, India.

(3) L. Bauer, D. Dhawan and C. S. Mahajanshetti, *J. Org. Chem.*, **31**, 2491 (1966).

(4) L. Bauer and C. S. Mahajanshetti, *J. Heterocyclic Chem.*, **4**, 325 (1967).

(5) A similar downfield shift was experienced by the 1-methyl protons when in 1-methylpyrazole, when flanked by a C=O group. For example, 1,3,5-trimethylpyrazole and ethyl 1,3-dimethyl-5-pyrazolecarboxylate showed N-$CH_3$ signals at $\delta$ 3.66 and 4.11 (in deuteriochloroform), respectively. [J. Elguero, R. Jacquier and H. C. N. Tien Duc, *Bull. Soc. Chim. France*, 3727 (1966)]. Also, the *N*-methyl proton signal in 7-methylhypoxanthine was deshielded ($\delta$ 4.05) compared to that of the 9-isomer ($\delta$ = 3.65, both in deuterium oxide; J. L. Long and D. S. Fuchs, *J. Chem. Soc., Perkins I*, 1284 (1974).

(6) K. H. Kleine, G. Gräfe and R. Haller, *Arch. Pharm.*, **302**, 16 (1969).

(7) D. Lichtenberg, F. Bergmann and Z. Neiman, *J. Chem. Soc.*, C, 1676, 1939, 1822 (1971).

(8) O. Somorin, *J. Gen. Chem., USSR*, **43**, 1851 (1973).

(9) H. Rasmussen and E. Sletten, *Acta. Chem. Scand.*, 27, 2757 (1973).

(10) D. Leonov and D. Elad, *J. Org. Chem.*, **39**, 1470 (1974).

(11) T. Fujii, T. Sato and T. Itaya [*Chem. Pharm. Bull. Japan*, **19**, 1731 (1971)] showed that the methyl signal in 1-methoxyadenine appeared at $\delta$ 3.84 (DMSO).

(12) For their synthesis, see Ref. 3, 4 and P. Schmidt, K. Eichenberger, M. Wilhelm and J. Druey, *Helv. Chem. Acta*, **42**, 349 (1959).

(13) V. Papesch and R. M. Dodson, *J. Org. Chem.*, **30**, 199 (1965).

(14) E. B. Dennler, C. R. Portal and A. R. Frasca, *Spectrochim. Acta*, **23A**, 2243 (1967).