of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JOC-75-1815.

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(21) Although the compound presumed to be 4-amino-1-(β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine has been shown to be a substrate for certain adenosine-utilizing enzymes, e.g., adenosine deaminase[22] and adenosine kinase,[23] the isomeric ribofuranoside has not been tested for comparative purposes. Since it has been shown that isoadenosine [6-amino-3-(β-D-ribofuranosyl)purine] is a (weak) substrate for adenosine deaminase[24] and adenosine kinase,[23] it was obviously important to compare the activities of isomers **12** and **13** in bioassays before using the results to assign structures.
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A Chemical and Carbon-13 Nuclear Magnetic Resonance Reinvestigation of the *N*-Methyl Isomers Obtained by Direct Methylation of 5-Amino-3,4-dicyanopyrazole and the Synthesis of Certain Pyrazolo[3,4-*d*]pyrimidines[1]

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A reinvestigation of the structural assignments for the isomeric *N*-1- and *N*-2-methyl derivatives of 5-amino-3,4-dicyanopyrazole (**1**), obtained by direct methylation, according to the published procedure, has been accomplished. The higher melting isomer (**2**, mp 243–245°) was annulated to give 4-amino-3-cyano-1-methylpyrazolo[3,4-*d*]pyrimidine (**4**) and alkaline peroxide converted **4** into 4-amino-1-methylpyrazolo[3,4-*d*]pyrimidine-3-carboxamide (**7a**). Hydrolysis of the cyano group of **4** under more vigorous conditions gave 4-amino-1-methylpyrazolo[3,4-*d*]pyrimidine-3-carboxylic acid (**7b**), which was subsequently decarboxylated in hot sulfolane to afford 4-amino-1-methylpyrazolo[3,4-*d*]pyrimidine (**7c**) of established structure. This established the structure of the *N*-methylpyrazole (mp 243–245°) as 5-amino-3,4-dicyano-1-methylpyrazole (**2**) and reversed the structural assignment previously reported for **2**. A similar reaction sequence converted the lower melting isomer (**3**, mp 128–130°) into 4-amino-2-methylpyrazolo[3,4-*d*]pyrimidine (**8d**) and established the structure of **3** as 5-amino-3,4-dicyano-2-methylpyrazole. ^{13}C NMR spectroscopy has furnished additional corroboration for these structural reassignments.

We have been involved for some time in the synthesis of nucleosides which are related to the naturally occurring pyrazolo[4,3-*d*]pyrimidine nucleosides[2] formycin and formycin B and the pyrrolo[2,3-*d*]pyrimidine nucleosides[3a] tubercidin, toyocamycin, and sangivamycin. The significant antitumor activity reported[3b] for these nucleoside antibiotic analogs (vide supra) prompted us to extend our investigation into the pyrazolo[3,4-*d*]pyrimidine area. It was during this phase of our research that we synthesized a ribofuranosyl derivative of 4-amino-3-cyanopyrazolo[3,4-*d*]pyrimidine (**12**).[4] This required the preparation of the *N*-1- and *N*-2-methyl derivatives of 4-amino-3-cyanopyrazolo[3,4-*d*]pyrimidine (**12**) so that an unequivocal assignment for the site of ribosylation could be made on the basis of uv spectral data.[5,6] However, a survey of the literature revealed that these *N*-methyl derivatives of **12** had not yet been reported. The most obvious approach to the synthesis of these desired model methyl compounds appeared to be a ring closure of the known[7] *N*-1- and *N*-2-methyl derivatives[8] of 5-amino-3,4-dicyanopyrazole (**2** and **3**, respectively). However, assignments[7] for the actual sites of methylation for **2** and **3** were found on closer examination to be equivocal and this prompted us to initiate the present study which was designed to unequivocally establish the actual sites of methylation.[5]

It was reported that the reaction of methylhydrazine with tetracyanoethylene gave a single *N*-methyl derivative of 5-amino-3,4-dicyanopyrazole which was reported[7] to be the *N*-1-methyl derivative **2**. On the other hand, reaction of 5-amino-3,4-dicyanopyrazole (**1**) with dimethyl sulfate was

found[7] to yield two *N*-methyl derivatives, a lower melting isomer (128–130°) that was identical with the product obtained from the reaction between methylhydrazine and tetracyanoethylene (assigned[9] structure **2**) and a higher melting isomer (mp 243–245°) which was assigned the structure 5-amino-3,4-dicyano-2-methylpyrazole (**3**).

It is of considerable interest that a series of *N*-methyl-4-alkylaminopyrazolo[3,4-*d*]pyrimidines was recently prepared[10] using the *N*-methylpyrazole derivative obtained from the reaction between methylhydrazine and tetracyanoethylene as the starting material. The authors of this work also assigned[10] the position of attachment of the methyl groups as being at N-1 on the basis of the previous report.[7]

We have synthesized the isomeric *N*-methyl-5-amino-3,4-dicyanopyrazoles according to published procedures[7] and have established, through a series of chemical conversions, that the original structural assignments are incorrect and should be reversed. These structural reassignments have been corroborated by carbon-13 nuclear magnetic resonance spectroscopy.

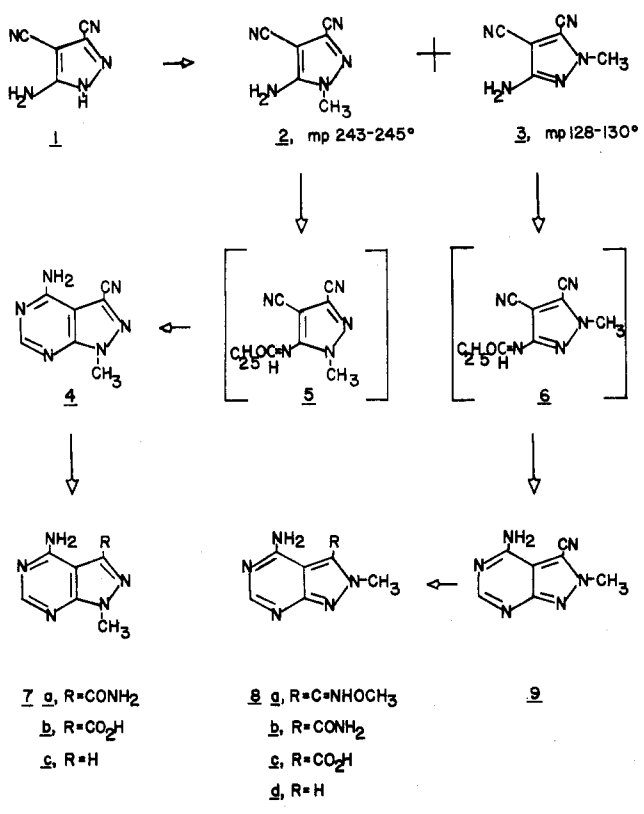
Chemical Evidence for Structure Assignments. Reaction of 5-amino-3,4-dicyanopyrazole (**1**) with dimethyl sulfate and aqueous sodium hydroxide yielded a mixture of isomers that were separated by fractional crystallization. The higher melting isomer (**2**) (vide infra) had mp 243–245° (47% yield) and the lower melting isomer (**3**) had mp 128–130° (8% yield). The lower melting isomer was found

$$1 \longrightarrow \text{A (mp 243-245°)} + \text{B (mp 128-130°)}$$

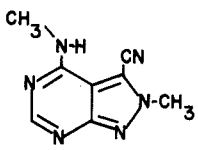
$$CH_3NHNH_2 + \begin{matrix} NC & & CN \\ & C{=}C & \\ NC & & CN \end{matrix} \longrightarrow \text{B (mp 128-130°)}$$

to be identical with the product obtained on reaction of methylhydrazine with tetracyanoethylene as had been previously reported.[7]

Reaction of the higher melting isomer (**2**) with diethoxymethyl acetate yielded a syrupy ethoxymethylene derivative (**5**) which was ring closed during treatment with methanolic ammonia to yield a compound for which we assigned the structure 4-amino-3-cyano-1-methylpyrazolo[3,4-*d*]pyrimidine (**4**) on the basis of the following: treatment of **4** with ammonium hydroxide and hydrogen peroxide resulted in the formation of the carboxamide **7a** (72% yield); alkaline hydrolysis of **4**, under more vigorous conditions, gave a good yield of the carboxylic acid **7b** which was subsequently decarboxylated in hot (215–220°) sulfolane[11] to provide pure 4-amino-1-methylpyrazolo[3,4-*d*]pyrimidine (**7c**), mp 267–269°. The ir, ^{1}H NMR, and uv spectral data for **7c** were identical with those of an authentic sample of **7c** prepared by a different route[12] and a mixture melting point was undepressed.



The corresponding series of 2-methyl compounds was prepared for comparative purposes. Treatment of the lower melting isomer (**3**, mp 128–130°) with hot diethoxymethyl acetate furnished the crystalline ethoxymethylene derivative **6** with mp 98–100.5°, which was the same melting point as that previously reported[10] for the ethoxymethylene derivative of the other isomer "1-methyl-5-amino-3,4-dicyanopyrazole". Reaction of **3** with *N*-methylformamide at reflux temperature yielded a compound for which we have unequivocally assigned the structure 3-cyano-2-methyl-4-methylaminopyrazolo[3,4-*d*]pyrimidine (**10**). It is



10

of interest that **10** has a uv spectrum[13] and melting point identical with those previously reported[10] for "3-cyano-1-methyl-4-methylaminopyrazolo[3,4-*d*]pyrimidine". It was found that brief (1 hr or less) treatment of the ethoxymethylene derivative **6** with methanolic ammonia did not result in the formation of 4-amino-3-cyano-2-methylpyrazolo[3,4-*d*]pyrimidine (**9**) as we had expected on the basis of obtaining **4** from **5** under similar reaction conditions. Instead, a product was isolated whose elemental analysis indicated that we had obtained the desired heterocycle (**9**) plus 1 mol of methanol (by solvation or covalently bound). The ^{1}H NMR spectrum contained peaks at δ 3.94 and 4.25 (singlets) which were assigned to methyl groups. In addition, the ir spectrum revealed the absence of a band in the 2237–2222-cm^{-1} region, which was additional substantiation that a reaction had occurred at the cyano group. On the basis of the above data, this compound was assigned the structure methyl 4-amino-2-methylpyrazolo[3,4-*d*]pyrimidine-3-formimidate (**8a**). This prompted us to modify our reaction conditions and it was subsequently found that 4-amino-3-cyano-2-methylpyrazolo[3,4-*d*]pyrimidine (**9**) could be formed in high yield by treating the crystalline ethoxymethylene derivative (**6**) with liquid ammonia at room temperature for 16 hr. As would be expected from the above observation, the cyano group of 4-amino-3-cyano-2-methylpyrazolo[3,4-*d*]pyrimidine (**9**) was very reactive and a facile conversion of **9** to the corresponding carboxamide (**8b**) was observed on treatment with alkaline hydrogen peroxide. Hydrolysis of the cyano group with aqueous sodium hydroxide proceeded smoothly [ca. five times faster than the corresponding 1-methyl isomer (**4**)] to give a high yield (91%) of the carboxylic acid **8c**. Decarboxylation of **8c** in hot sulfolane was very rapid [approximately 25 times faster than the decarboxylation of 4-amino-1-methylpyrazolo[3,4-*d*]pyrimidine-3-carboxylic acid (**7b**)] and provided a 41% yield of 4-amino-2-methylpyrazolo[3,4-*d*]pyrimidine (**8d**), mp 346–348° dec. It was subsequently found that a

better yield of **8d** could be obtained by sublimation[14] of **8c**. A comparison (uv, ir, mixture melting point) of **8d** with an authentic sample[15] of 4-amino-2-methylpyrazolo[3,4-*d*]pyrimidine established that they were identical. This conversion of **2** and **3** to compounds of unequivocal structure (**7c** and **8d**, respectively) has unequivocally established the

Table I
Uv Spectral Data for Certain Pyrazoles and Pyrazolo[3,4-*d*]pyrimidines

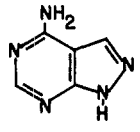
		pH 1		Methanol		pH 11	
No.	Compd	λ max	λ min	λmax	λmin	λmax	λmin
1	5-Amino-3,4-dicyano-pyrazole	273.0 (5.10)[a]	246.0 (2.74)	273.5 (3.83)	246.5 (2.56)	276.5 (6.76) 245.0 (10.6)	264.5 (6.22) 235.0 (9.31)
2	5-Amino-3,4-dicyano-1-methylpyrazole	275.0 (5.02)	248.5 (2.28)	275.5 (5.07)	247.0 (2.16)	275.0 (4.90)	248.5 (2.54)
3	5-Amino-3,4-dicyano-2-methylpyrazole	300.0 (4.66) 238.0 (9.77)	262.0 (1.73) 229.0 (8.76)	310.0 (4.86) 240.0 (10.1)	265.0 (1.05) 231.0 (9.10)		
12	4-Amino-3-cyanopyrazolo[3,4-*d*]pyrimidine	271.0[b] 264.5 (10.0) 236.0[b] 230.5[b]	246.0 (7.03)	287.0[b] 279.0 (10.6) 238.0[b]	248.0 (4.56)	294.5 (10.5) 288.5[b] 242.0 (14.4)	260.0 (6.89) 233.0 (11.5)
4	4-Amino-3-cyano-1-methylpyrazolo[3,4-*d*]-pyrimidine	267.5 (12.5) 233.5 (19.0) 227.0 (19.0)	249.0 (8.41) 230.5 (1.84) 221.5 (16.9)	294.0[b] 284.5 (14.4) 242.0[b] 237.0 (11.7)	251.5 (5.43) 226.0 (9.66)	293.0[b] 285.0 (14.5) 242.5[b] 237.5 (12.1)	252.0 (6.04) 229.5 (9.21)
9	4-Amino-3-cyano-2-methylpyrazolo[3,4-*d*]-pyrimidine	309.5[b] 296.5 (12.7) 273.5[b] 265.5[b] 241.5 (12.7) 236.0[b]	254.0 (8.34) 225.5 (11.3)	308.5 (11.2) 277.0[b] 267.5 (7.36) 248.0 (10.1)	282.5 (6.51) 260.0 (7.00) 238.0 (9.52)	304.5 (10.5) 275.0 (6.85) 266.5 (6.81) 246.0 (9.54)	281.5 (6.24) 271.0 (6.44) 257.5 (6.15) 236.0 (8.65)
10	3-Cyano-2-methyl-4-methylaminopyrazolo-[3,4-*d*]pyrimidine	316.0[b] 305.5 (13.5) 298.5 (13.2) 248.0 (8.85) 232.5[b]	300.0 (13.0) 258.0 (7.90) 237.5 (8.66)	316.0[c] (10.7) 254.0[c] (9.04) 230.0[b,c]	284.5 (5.20) 243.5 (7.46)	312.5 (10.6) 278.0[b] 268.5[b] 253.5 (8.80) 234.0[b]	284.5 (5.27) 242.0 (7.22)
7a	4-Amino-1-methylpyrazolo[3,4-*d*]pyrimidine-3-carboxamide	265.0 (9.11) 229.0 (15.0)	252.5 (8.06)	282.5 (9.21) 239.5 (11.1)	256.5 (6.53)	283.5 (9.12) 242.0 (9.60)	258.0 (5.95) 222.0 (4.04)
8b	4-Amino-2-methylpyrazolo[3,4-*d*]pyrimidine-3-carboxamide	279.0 (7.55) 233.0 (7.34)	251.5 (4.23)	300.0 (7.99) 244.0 (6.68)	260.5 (4.84) 237.0 (6.34)	296.0 (8.30) 239.0 (6.34)	258.0 (5.00) 235.0 (6.28)
8a	Methyl 4-amino-2-methylpyrazolo[3,4-*d*]pyrimidine-3-formimidate	279.5 (10.1) 242.5 (8.65)	255.5 (6.95) 228.0 (7.42)	305.0 (9.69) 253.0 (8.00)	266.5 (6.60) 238.0 (6.10)	302.5 (9.74) 247.0 (8.14)	276.0[b] 260.0 (6.18) 235.5 (7.11)
7b	4-Amino-1-methylpyrazolo[3,4-*d*]pyrimidine-3-carboxylic acid	265.5 (10.5) 231.5 (15.5)	250.5 (8.34) 222.5 (14.2)	292.0[b] 282.0 (11.4) 277.0[b] 236.0 (10.4)	252.5 (6.60) 236.0 (9.38)	292.0[b] 282.5 (11.1) 276.5[b] 238.0 (10.2)	252.5 (6.21) 230.5 (8.61)
8c	4-Amino-2-methylpyrazolo[3,4-*d*]pyrimidine-3-carboxylic acid	278.0 (10.5) 242.0[b] 235.5 (11.8) 287.0[b]	252.0 (7.34) 223.5 (10.0)	298.0[b] 290.0 (10.3) 279.0[b] 240.0 (10.4)	256.0 (7.21) 228.0 (9.34)	298.0 (10.7) 290.5[b] 277.5[b] 267.0[b] 242.5 (8.73)	257.5 (6.04) 231.5 (6.99)
11	4-Aminopyrazolo-[3,4-*d*]pyrimidine	258.0 (11.3)	238.5 (6.80)	281.0[b] 271.5 (11.3) 260.0[b]	235.0 (4.21)	280.0[b] 263.0 (10.6)	239.5 (6.93)
7c	4-Amino-1-methylpyrazolo[3,4-*d*]pyrimidine	258.0 (10.5)	240.5 (7.00)	286.5[b] 276.5 (11.2) 272.0[b] 260.5 (10.2)	265.0 (9.44) 239.0 (4.25)	286.0[b] 276.5 (11.2) 260.0 (11.1)	266.0 (10.4) 239.0 (5.32)
8d	4-Amino-2-methylpyrazolo[3,4-*d*]pyrimidine	266.5 (11.7)	241.0 (4.81)	298.0[b] 288.0 (12.9) 281.0[b] 267.0 (8.70) 259.5[b] 235.0[b] 230.0 (7.88)	270.0 (8.62) 242.5 (2.89) 224.5 (6.99)	296.0[b] 286.5 (12.5) 279.0[b] 266.5 (9.34) 258.0[b] 233.0[b]	269.5 (9.16) 241.5 (3.70)

[a] Values in parentheses are $\epsilon \times 10^{-3}$. [b] Shoulder. [c] Sample dissolved in ethanol.

structures for all compounds reported herein and has also established that the previous structural assignments[7,10] for certain compounds were in error.

From the uv absorption data (Table I) for the methylated pyrazoles and pyrazolo[3,4-*d*]pyrimidines, it is seen that for each pair of isomeric compounds (at all pH ranges) the *N*-2-methyl isomer shows its principal absorption maximum at a longer wavelength than the *N*-1-isomer. This relationship has been reported[16] for various N-substituted pyrazolo[3,4-*d*]pyrimidines. This trend appears to be general for the pyrazolo[3,4-*d*]pyrimidines and is most likely due to the different type of electronic structures for the two isomers. However, in the case of the N-substituted pyrazoles this difference needs further substantiation which precludes the use of this trend as a basis for the unequivocal assignment of the site of N-alkylation.

For comparison purposes, the uv spectral data for 5-amino-3,4-dicyanopyrazole (1), 4-aminopyrazolo[3,4-*d*]pyrimidine (**11**), and 4-amino-3-cyanopyrazolo[3,4-*d*]pyrimidine (**12**) have been included in Table I. It is of considerable interest that the positions of uv maxima (pH 1 and methanol spectra) for **1, 11,** and **12** are very similar to the values shown for the corresponding *N*-1-methyl derivatives (**2, 7c,** and **4,** respectively) and very dissimilar for the corresponding *N*-2-methyl derivatives (**3, 8d,** and **9,** respectively). Since the uv spectral data for the unsubstituted heterocycles more closely resemble the spectral data for the *N*-1-methyl derivatives this would strongly suggest that the nonalkylated heterocycles exist predominantly in the tautomeric forms shown. ^{13}C NMR spectroscopy also provides data to support this assumption (vide infra).



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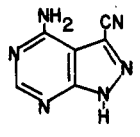

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Structure Assignments Based on ^{13}C NMR Spectral Data. In order to supplement and corroborate the structural assignments based on chemical evidence and presented in the previous section, carbon-13 nuclear magnetic resonance (^{13}C NMR) spectral data was obtained on compounds **4, 7c, 9, 8d, 11,** and **12.** The value of ^{13}C NMR spectroscopy in elucidating molecular structure is well known[17] and previous studies carried out in this laboratory,[18-25] as well as others,[26] have demonstrated the value of ^{13}C NMR as a tool in determining the site of N substitution in nitrogen heterocycles. If one compares the ^{13}C NMR spectral data of a nitrogen heterocycle with a N-alkylated derivative of this heterocycle (where the N substitution is methyl or β-D-ribofuranosyl), chemical shift changes are observed which reflect the replacement of a proton by a substituent on a specific nitrogen atom with the concomitant absence of tautomeric structures. While the magnitude of the N-substituent parameters is affected by the nature of the substituent (i.e., H, CH_3, or ribose),[25] the authors are aware of no case where the carbon adjacent (α) to the site of N substitution fails to move upfield or, conversely, fails to move downfield when the substituent is removed.[27] Rapid proton exchange among the various tautomeric species complicates the structural analysis but tautomeric populations have now been derived for a number of species including 26 derivatives of purines and pyrrolo[2,3-*d*]pyrimidines.[25a]

In order to independently verify the structures of **4** and **9** we also examined **12** and compared the ^{13}C NMR spectral data of these three compounds with **7c, 8d,** and 4-aminopyrazolo[3,4-*d*]pyrimidine (**11**). The structures for **7c, 8d,** and **11** have been reliably determined by chemical techniques.

Table II
Carbon-13 Chemical Shifts[a] for Derivatives of 4-Aminopyrazolo[3,4-*d*]pyrimidine

Compd[b]	Carbon position						
	C-3	C-3a	C-4	C-6	C-7a	CN	CH_3
4-APP riboside[c]	133.41	100.61	158.16	156.21	154.14		
11	132.33	99.65	158.18	154.70	154.70		
7c	132.23	100.05	158.33	155.24	153.01		32.38
8d	124.91	102.23	159.28	155.61	160.17		39.45
12	115.55	100.45	156.99	156.32	155.10	113.17	
4	115.14	100.75	157.19	156.50	153.42	112.38	33.78
9	106.62	104.14	157.69	156.40	159.48	109.21	39.54

[a] Taken with respect to external Me_4Si. Chemical shift values were measured relative to internal dioxane and converted to the Me_4Si scale using $\delta_{Me_4Si} = \delta_{dioxane} - 17.5 \times 10^{-4}T(°C) - 66.32$ ppm. [b] Samples were dissolved in HMPT (200 mg/3.0 ml solvent except **8d**, where the solution was 84 mg/3.0 ml). [c] See ref 23.

Table III
Changes[a] in the Carbon-13 Chemical Shifts ($\Delta\delta$)[b] for Certain Pyrazolo[3,4-*d*]pyrimidines

Compds compared		Δδ					
i	j	C-3	C-3a	C-4	C-6	C-7a	CN
11	7c	0.10	−0.40	−0.15	−0.54	1.69	
11	8d	7.42	−2.58	−1.10	−0.91	−5.47	
12	4	0.41	−0.30	−0.20	−0.18	1.68	+0.79
12	9	8.93[c] (6.55)[d]	−3.69	−0.70	−0.08	−4.38	+3.96[c] (6.34)[d]
11	12	16.78	0.80	1.19	−1.62	−0.40	

[a] Negative numbers represent shift changes (in parts per million) to lower field as compared to the chemical shifts observed for the corresponding positions in the reference compound. [b] $\Delta\delta = \delta C_i - \delta C_j$. [c] Preferred assignment. [d] Parenthetical numbers are the values obtained if the chemical shift values for C-3 and CN (of **12**) are reversed.

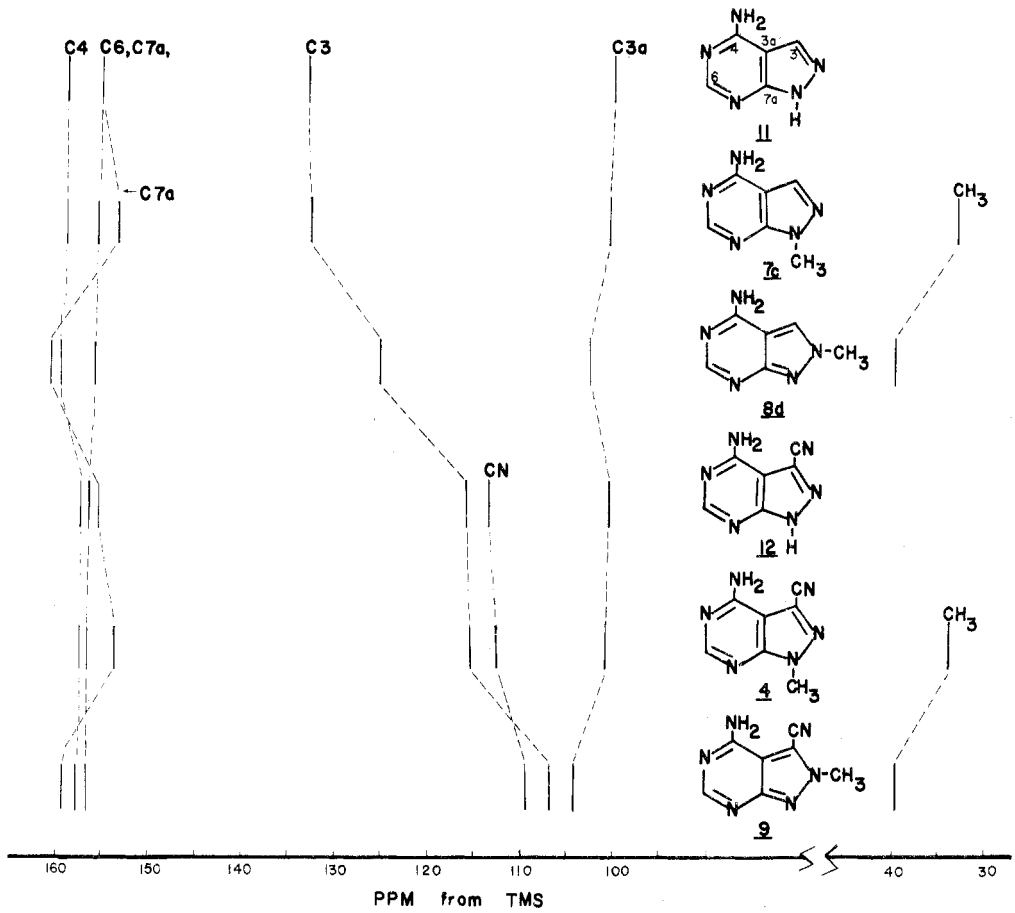

Figure 1. Carbon-13 resonance patterns for certain pyrazolo[3,4-*d*]pyrimidines.

The chemical shifts of **11** are given in Table II and the shift assignments were made by a comparison of the shift values for **11** with the shift values observed for 4-amino-1-(β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine (4-APP riboside).[23] It is interesting to note that C-6 has moved 1.5 ppm upfield in **11** (compared to 4-APP riboside) and is accidentally degenerate with **7a** (verified by off-resonance decoupling). The *N*-1-methyl derivative of **11** (**7c**) exhibits only minor chemical shift variations when compared to **11** (and 4-APP riboside) as shown in the correlation diagram (Figure 1). The chemical shifts of the compound identified as **8d** exhibits two major chemical shift variations when compared to the chemical shifts of **11.** The shift changes $\Delta\delta$ ($\delta C_i - \delta C_j$) given in Table III at C-3 and C-7a are in opposite directions and are consistent with addition of an α-substituent shift at C-3 and removal of the α-substituent effect at C-7a. While the magnitudes of the shift changes noted for C-3 and C-7a in Table III (7.42 and −5.47 ppm, respectively) are not identical with the +9.64 ppm α shift observed in simple five-member heterocycles,[20] the values are qualitatively correct. By comparing the data for **7c** and **8d** with that of **11,** one can readily conclude that the structure assignments are correct, since a reversal in structures would cause the resonance positions of C-3 and C-7a to move in opposite directions to that observed in the data.

Similar comparisons can be made among **12, 4,** and **9.** The resonance positions of C-4, C-6, C-7a, and C-3a in **12** were determined by off-resonance decoupling (C-6) and with the aid of the correlation diagram. The assignments of C-3 and the cyanocarbon resonance positions could not be determined unequivocally and may be reversed. However, when comparing the proton coupled and decoupled spectra of **12,** one observes that one of the resonance lines of the pair in question is little affected while the other is significantly broadened and decreases substantially in intensity when the proton decoupler is turned off. The resonance position exhibiting broadening is thus tentatively assigned to C-3, since long-range proton–carbon coupling (two-bond and three-bond coupling from the labile proton) is more likely to occur at C-3 than at the cyano carbon. It is also noted that C-3 in **12** is shifted 16.78 ppm to higher field than the corresponding position in **11.** This shift change is consistent with the 16.4 ppm upfield shift for the C-1 carbon in benzonitrile[28] (as compared to the resonance peak observed for benzene) and is further evidence that the resonance peaks for C-3 and –CN of **12** are correctly assigned.

The resonance positions in **4** exhibit little variation from **12** and the differences, $\Delta\delta$, given in Table III are quite similar, position for position, for the **7c, 11** and the **4, 12** pairs of compounds. The variations in the resonance positions of **9** as compared to **12** can also be compared to the variations observed for the **8d, 11** pair (given in Table III). Once again the $\Delta\delta$ values are comparable between the **8d, 11** and the **9, 12** pairs. As observed in the known structures **11** and **8d,** comparison of **9** and **12** indicates that the methyl resides at N-2, since C-3 is shifted upfield 8.93 ppm and C-7a moves 4.38 ppm to lower field. The same qualitative results are obtained even if the shift assignments at C-3 and CN are reversed. Hence, the ^{13}C NMR spectral data confirms the chemical evidence for the structures assigned to **4** and **9.**

In Figure 1, one observes that resonance peaks for the methyl carbons fall into two patterns. The methyl carbons, of the two *N*-1-methyl species, are separated by 1.4 ppm and are found upfield from the methyl carbons of the *N*-2-methyl derivatives which vary by only 0.1 ppm in their resonance positions. The variation in methyl chemical shifts apparently reflects the difference in resonance structures of the N-1 and N-2 methylated compounds, and these reso-

nance effects are transferred in part to the exocyclic group. It is also interesting to note that the resonance peak for the nitrile carbon moves upfield 0.79 and 3.96 ppm in **4** and **9**, respectively, as compared to the nitrile carbon of **12**. The chemical shift change of the nitrile carbon of **9** may likewise reflect the differences between the resonance structures of **4** and **9**.

Conclusions

The work presented herein has established on the basis of new chemical evidence and ^{13}C NMR spectral data that the original structural assignments for **2** and **3** were reversed. This dual approach has proven to be very useful in complex structure characterization studies in this and other laboratories and promises to become even more important in the future as the powerful ^{13}C NMR techniques become more widely used.

Experimental Section

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Proton magnetic resonance spectra were obtained with a Varian A-60 spectrometer with DSS (sodium 2,2-dimethyl-2-silapentane-5-sulfonate) as internal standard and the chemical shifts are expressed as δ, parts per million, from DSS with DMSO-d_6 as solvent. Carbon-13 nuclear magnetic resonance spectra were obtained with a Varian XL-100-15 spectrometer equipped with a 620-F computer. The infrared spectra were determined, utilizing pressed KBr disks, with a Beckman IR-8 spectrophotometer; absorptions are given in reciprocal centimeters and are strong absorptions unless otherwise noted. Ultraviolet spectra were recorded with a Beckman DK-2 spectrophotometer and absorptions are expressed in nanometers. Elemental analyses were performed by Heterocyclic Chemical Corp., Harrisonville, Mo., and M-H-W Laboratories, Garden City, Mich.

5-Amino-3,4-dicyano-1-methylpyrazole (2) and 5-Amino-3,4-dicyano-2-methylpyrazole (3). 5-Amino-3,4-dicyanopyrazole[7] (**1**, 66.5 g, 0.50 mol) was added with stirring to a solution of sodium hydroxide (23.0 g, 0.580 mol) in water (100 ml) to effect a clear solution. Dimethyl sulfate (85 g, 0.67 mol) was added immediately after **1** had completely dissolved. The reaction mixture was stirred at room temperature for 15 min, and the solid that had separated was collected by filtration, washed with cold water (2 × 20 ml), and dried (25°, 0.5 Torr), yield 45.0 g. The dry material (45 g) was added to ethanol (200 ml), the mixture was heated at reflux temperature, and the undissolved solid was removed from the hot mixture by filtration. The filter cake was recrystallized from dioxane to obtain 5-amino-3,4-dicyano-1-methylpyrazole (**2**) as colorless needles: mp 241–244° [lit.[7] mp 243–245°]; yield 35.0 g (47.5%); ir[29] 3448, 3378, 3247 (NH); 2242 (C≡N); 1647, 1658, 1650, 1433 cm^{-1} (NH and C=N); ^1H NMR[30] δ 3.59 (s, 3 H, CH_3), 7.06 (s, 2 H, NH_2).

The ethanol filtrate, from above, deposited more solid upon standing (25°, 1 hr) which was collected by filtration and washed with a small amount of cold water. The air-dried filter cake was recrystallized from ethanol to obtain 5-amino-3,4-dicyano-2-methylpyrazole (**3**) as needles: mp 128–130° [lit.[7] mp 128–130°]; yield 6.0 g (8.2%); ir 3472, 3367 (NH); 2232 (C≡N); 1621, 1546, 1517 cm^{-1} (NH and C=N); ^1H NMR δ 3.78 (s, 3 H, CH_3), 6.14 (s, 2 H, NH_2).

5-Amino-3,4-dicyano-2-methylpyrazole (3). Tetracyanoethylene (12.8 g, 0.1 mol) was added slowly to a solution of methyl hydrazine (4.6 g, 0.1 mol) in water (200 ml) at 0° with efficient stirring. After the addition was completed, the reaction mixture was stirred for 1 hr at 0° and then heated at reflux temperature for 15 min. The brown reaction solution was allowed to stand at 5° for 8 hr and the crystalline solid that separated was collected by filtration and washed several times with ice-cold water. The residue was air dried and then recrystallized from ethanol as needles to yield 7.0 g (47.6%) of **3**, mp 130–131°. A mixture melting point of this product with the sample of **3** obtained from the methylation of 5-amino-3,4-dicyanopyrazole was undepressed and their uv spectra were found to be identical.

4-Amino-3-cyano-1-methylpyrazolo[3,4-*d*]pyrimidine (4). 5-Amino-3,4-dicyano-1-methylpyrazole (**2**, mp 243–245°, 4.0 g) was heated in diethoxymethyl acetate (25 ml) for 2.5 hr at reflux temperature and under anhydrous conditions. The pale orange solution was evaporated (bath temperature 50°) under reduced pressure to a syrup. The syrup was dissolved in dry toluene (50 ml) and again evaporated in vacuo to a syrup. This process was repeated four times to provide the dry, syrupy 5-ethoxymethylene derivative (**5**). This syrup was dissolved in 200 ml of methanolic ammonia (methanol saturated with ammonia at 0°) and allowed to stand for 18 hr at room temperature. The solid that had separated was collected by filtration, washed with cold (10°) methanol (2 × 10 ml), and recrystallized from dimethylformamide as microneedles to yield 3.5 g (74.0%) of **4**: mp 312° dec; ir 3472, 3356 (w) (NH); 2242 (w) (C≡N); 1621, 1538 cm^{-1} (NH, C=N, and C=C).

Anal. Calcd for $C_7H_6N_6$: C, 48.28; H, 3.44; N, 48.28. Found: C, 47.88; H, 3.67; N, 48.24.

Methyl 4-Amino-2-methylpyrazolo[3,4-*d*]pyrimidine-3-formimidate (8a). 5-Amino-3,4-dicyano-2-methylpyrazole (**3**, mp 128–130°, 6.0 g) was heated in diethoxymethyl acetate (30 ml) at reflux temperature for 3 hr with exclusion of moisture. The dark brown solution was evaporated in vacuo (bath temperature 50°) to a syrup. The syrup was dissolved in dry toluene (50 ml) and again evaporated in vacuo to dryness. This procedure was repeated four times to furnish the crystalline 5-ethoxymethylene derivative[31] (**6**), which was dissolved in 300 ml of methanolic ammonia and allowed to stand at room temperature for 18 hr. The solid that had separated was collected by filtration and washed with cold (0°) methanol (2 × 10 ml) and the filter cake was recrystallized from aqueous ethanol as long, colorless needles to yield 5.70 g (80%) of **8a**: mp 280° dec; ir 3195 (NH); 1645, 1590, 1527, 1481 (NH, C=N, and C=C); ^1H NMR δ 3.94 (s, 3 H, NCH_3), 4.25 (s, 3 H, OCH_3), 7.55 (br s, 2 H, $-NH_2$), 8.20 (s, 1 H, H_6), 9.06 (s, 1 H, C=NH).

Anal. Calcd for $C_8H_{10}N_6O$: C, 46.60; H, 4.85; N, 40.78. Found: C, 46.77; H, 4.82; N, 41.02.

4-Amino-3-cyano-2-methylpyrazolo[3,4-*d*]pyrimidine (9). The crude, crystalline 5-ethoxymethylene derivative, **6** (prepared from 6.0 g of **3**) was dissolved in liquid ammonia (100 ml) and the reaction mixture was allowed to stand at room temperature for 16 hr in a sealed stainless steel reaction vessel. The reaction mixture was then evaporated to dryness in vacuo and the solid was recrystallized from dimethylformamide as pale yellow microneedles to yield 5.0 g (70.5%) of **9**: mp 280° dec; ir 3472 (w), 3356 (NH); 2247 (m) (C≡N); 1621, 1538 cm^{-1} (NH, C=N, C=C); ^1H NMR δ 4.75 (s, 3 H, CH_3), 7.56 (br s, 2 H, NH_2), 8.34 (s, 1 H, H_6).

Anal. Calcd for $C_7H_6N_6$: C, 48.28; H, 3.44; N, 48.28. Found: C, 48.42; H, 3.52; N, 48.40.

4-Amino-1-methylpyrazolo[3,4-*d*]pyrimidine-3-carboxamide (7a). Hydrogen peroxide (4.0 ml of 30% solution) was added in one portion to a stirred suspension of **4** (1 g) in concentrated aqueous ammonia (20 ml, room temperature). Stirring was continued for 2.5 hr, during which time **4** went into solution (0.5 hr), and this was soon followed by the appearance of a new white solid (1 hr). After 2 hr the solid was collected by filtration, washed well with cold water, and then air dried. The solid was recrystallized from methanol to yield 0.8 g (72.7%) of **7a** as colorless needles: mp 350° dec; ir 3390, 3247 (NH); 1639, 1616, 1580, 1471 cm^{-1} (C=O, NH, C=N, C=C).

Anal. Calcd for $C_7H_8N_6O$: C, 43.75; H, 4.16; N, 43.75. Found: C, 43.90; H, 4.51, N, 43.60.

4-Amino-2-methylpyrazolo[3,4-*d*]pyrimidine-3-carboxamide (8b). Hydrogen peroxide (4 ml of 30% solution) was added in one portion to a stirred suspension of **9** (1.0 g) in concentrated aqueous ammonium hydroxide (20 ml, room temperature). After 1 hr the reaction mixture became clear and then a solid began to separate from solution. After 4 hr the solid was collected by filtration, washed thoroughly with cold water, and then recrystallized from methanol to yield 0.5 g (45.3%) of **8b** as needles: mp 310° dec; ir 3390, 3012 (NH); 1592, 1473 cm^{-1} (C=O, NH, C=N, C=C); ^1H NMR δ 4.27 (s, 3 H, CH_3), 7.61 (br s, 2 H, NH_2), 8.43 (s, 1 H, H_6), 8.44 (br s, 2 H, $CONH_2$).

Anal. Calcd for $C_7H_8N_6O$: C, 43.75; H, 4.16; N, 43.75. Found: C, 43.60, H, 4.32; N, 43.50.

4-Amino-1-methylpyrazolo[3,4-*d*]pyrimidine-3-carboxylic Acid (7b). Aqueous sodium hydroxide (3.52 ml of 1.25 *M* solution, 4.4 mmol) was added to a suspension of **4** (700 mg, 4 mmol) in 15 ml of water and the suspension was heated at reflux temperature for 5 days (ammonia evolution ceased during this time). The solution was cooled to room temperature and 100 mg of white solid (mp >360°, insoluble in hot water) was removed by filtration. The clear filtrate was acidified by the addition of 4.32 ml of 1.02 *M* aqueous hydrochloric acid. A gelatinous precipitate formed that turned to a white powder on further stirring. The solid (610 mg, 78%) was redissolved (25°) in aqueous sodium hydroxide (3.52 ml of 1.25 *M* solution) and then reprecipitated by the addition of

aqueous hydrochloric acid (4.32 ml of 1.02 *M* solution). The white solid was collected by filtration and washed with cold (0°) water (3 × 5 ml) to yield 570 mg (73.4%) of **7b:** mp 336° dec (and sublimes); ir 3356 (NH); 2703–2439 (OH); 1701 (C=O); 1603, 1548 (w), 1513 cm^{-1} (w) (NH, C=N, C=C).

Anal. Calcd for $C_7H_7N_5O_2$: C, 43.53; H, 3.65; N, 36.26. Found: C, 43.31; H, 3.93; N, 35.96.

4-Amino-2-methylpyrazolo[3,4-*d*]pyrimidine-3-carboxylic Acid Hemihydrate (8c). When **9** (700 mg, 4 mmol) was treated as above, solution occurred in 3 min followed by the formation of a white precipitate in 5 min more which in turn soon dissolved. Ammonia evolution could no longer be detected after 36 hr at reflux temperature. Filtration was followed by the addition of aqueous hydrochloric acid, which caused 730 mg (91%) of **8c** to precipitate in the form of a white solid. A portion of the solid was dissolved in aqueous base and reprecipitated with aqueous acid to afford an analytical sample: mp 320–333° (bubbling, darkening at melting point with a change in crystalline form at 266°); ir 3846–2083 (NH, OH); 1695, 1634 (NH, C=N, C=C).

Anal. Calcd for $C_7H_7N_5O_2 \cdot 0.5H_2O$: C, 41.57; H, 3.99; N, 34.64. Found: C, 41.71; H, 4.11; N, 34.39.

4-Amino-1-methylpyrazolo[3,4-*d*]pyrimidine (7c). Dry nitrogen was passed through a suspension of **7b** (193 mg, 1 mmol) in dry, redistilled sulfolane (15 ml) for 0.5 hr. The flask containing the suspension was then lowered into a Woods metal bath preheated to 215–220° and the carbon dioxide evolution was monitored (CO_2 was led through a connecting tube to an inverted graduated cylinder, filled with water, for monitoring purposes). One-third of the carbon dioxide (7.6 ml) was evolved in ca. 25 min with the reaction being complete in ca. 100 min. No appreciable carbon dioxide evolution was observed at temperatures below 210°. Excess sulfolane was removed by vacuum distillation (0.1 Torr, oil bath at 70°). The semisolid residue was triturated with 40 ml of a 1:1 (v/v) methylene chloride–diethyl ether mixture, and then recrystallized from water (3 ml) to yield 80 mg (56%) of **7c,** mp 267–269°. A mixture melting point with an authentic sample[12] of **7c** (mp 266–268°) was undepressed. The ir, uv, and ^1H NMR spectra obtained for our product were superimposable with those obtained for an authentic sample of **7c:** ir 3300 (m), 3086 (NH); 1669, 1595, 1570, 1495 (w) (NH, C=N,.C=C); 1319 (m), 1190 (w), 1016 (w), 917 (m), 789 (m), 714 cm^{-1} (m).

4-Amino-2-methylpyrazolo[3,4-*d*]pyrimidine (8d). Method 1. Sublimation (235°, 0.3 mm) of **8c** (300 mg, 1.56 mmol) yielded 190 mg (82%) of **8d,** mp 341–343° (vigorous dec, darkens at 330°). One recrystallization of **8d** from water raised the melting point to 346–348° (vigorous dec) and a mixture melting point with an authentic sample[15] of 4-amino-2-methylpyrazolo[3,4-*d*]pyrimidine showed no depression. The ir and uv spectra obtained for our product were identical with those obtained for the authentic sample: ir 3311, 3030 (NH); 1661 (w), 1608, 1531 (NH, C=N, C=C); 1412 (w), 1342 (m), 1242, 1176 (m), 1034 (m), 990 (m), 909 (m), 872 (w), 791 cm^{-1}.

Method 2. 4-Amino-2-methylpyrazolo[3,4-*d*]pyrimidine-3-carboxylic acid (**8c,** 100 mg, 0.52 mmol) was decarboxylated in 4 ml of sulfolane at ca. 215° as described for the preparation of **7c.** Carbon dioxide evolution was complete (14 ml) in 3 min with one-third of the gas being evolved in less than 1 min. The usual work-up followed by recrystallization from water (3 ml) yielded 31.9 mg (41%) of pure **8d.**

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Registry No.—**1,** 54385-49-8; **2,** 50680-85-8; **3,** 54385-48-7; **4,** 42204-41-1; **7a,** 54814-48-1; **7b,** 54814-49-2; **7c,** 5334-99-6; **8a,** 54814-50-5; **8b,** 54814-51-6; **8c,** 54385-54-5; **8d,** 21230-48-8; **9,** 54814-52-7; **10,** 54814-53-8; **11,** 2380-63-4; **12,** 6826-96-6; 4-APP riboside, 58-61-7; tetracyanoethylene, 670-54-2; methyl hydrazine, 60-34-4; diethoxymethyl acetate, 14036-06-7.

References and Notes

(1) We wish to acknowledge support for this work by means of a grant from Research Resources, National Institutes of Health (RR-0574) and a research contract from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Department of Health, Education, and Welfare (NO1-CM-23710 and NO1-CM-43806).
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(7) C. L. Dickenson, J. K. Williams, and B. C. McKusick, *J. Org. Chem.,* **29,** 1915 (1964).
(8) Although the nomenclature is not systematic, the N-methylated pyrazoles will be named as 1- or 2-methyl derivatives of 5-amino-3,4-dicyanopyrazole in order to simplify the discussion.
(9) The authors[7] presented a very unclear and confusing account of their research. At one point they rationalized that the initial attack on tetracyanoethylene by methyl hydrazine would involve "the nitrogen to which the methyl is attached" to yield 1-methyl-5-amino-3,4-dicyanopyrazole (**2**) and they listed **2** in a table as being the product from this reaction. Yet at another point, in their discussion on the products from the methylation of 5-amino-3,4-dicyanopyrazole, they appear to reverse this structural assignment.
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(13) An authentic sample of **10,** provided by Dr. S. M. Hecht, proved to be essentially identical in all respects with the product we obtained using his published procedure. It should be noted, however, that owing to what we would assume to be a printing error in the original publication,[10] our uv spectral data (pH 11, 253 nm) for **10** (see Table I) are different from the values (pH 12, 262 nm) previously reported for **10.**
(14) It has been previously shown that 4-aminopyrazolo[3,4-*d*]pyrimidine-3-carboxylic acid is decarboxylated during sublimation; see E. C. Taylor and A. Abul-Husn, *J. Org. Chem.,* **31,** 342 (1966).
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(26) G. P. Kreishman, J. T. Witkowski, R. K. Robins, and M. P. Schweizer, *J. Am. Chem. Soc.,* **94,** 5894 (1972).
(27) At first glance, it would appear that this statement is contradicted by the work of J. Elguero, C. Marzin, and J. D. Roberts, *J. Org. Chem.,* **39,** 357 (1974). These authors studied pyrrole, pyrazole, imidazole, *s*-triazole, *v*-triazole, tetrazole, and their *N*-methyl analogs. When comparing the free base and the *N*-methyl base, downfield shifts were noted for both α and β carbons in pyrrole and imidazole. These results, however, simply reflect the differences in absolute magnitude of the proton and methyl substituent parameters (see ref 25a). The problem is further complicated by inclusion of the various tautomeric structures which exist in the di-, tri-, and tetrazoles for which insufficient data has been obtained to adequately paramaterize the substituent effects. However, a close examination of the data presented by Elguero et al. clearly demonstrates that N-substitution, whether by a proton or a methyl group, consistently produces an upfield α shift. While β shifts undoubtedly occur also, their magnitude is such (−1 to −2 ppm) as to be obscured by structural changes and variations in the H/methyl substituent effects.
(28) L. B. Johnson and W. C. Jankowsky, "Carbon-13 NMR Spectra", Wiley-Interscience, New York, N.Y., 1972, Spectrum No. 226.
(29) Notation: w = weak; m = medium.
(30) Notation: s = singlet; br s = broad singlet.
(31) The solid could be recrystallized from toluene to yield colorless crystals (80%), mp 98–100.5° (lit.[10] mp 98–99°).