N-ALKYLATION OF SUBSTITUTED PYRAZOLES AND PYRAZOLO[3,4-d]PYRIMIDINES WITH DIMETHYLFORMAMIDE DIETHYL ACETAL OR TRIETHYL ORTHOFORMATE

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The N-alkylation of some substituted pyrazoles and pyrazolo[3,4-d]pyrimidines with dimethylformamide diethyl acetal or triethyl orthoformate has been examined. Dimethylformamide diethyl acetal is more effective as an alkylating agent than triethyl orthoformate. Alkylation of 3-methoxycarbonylpyrazole gives a mixture of N-1- and N-2-ethyl derivatives. Alkylation of pyrazolo[3,4-d]pyrimidines takes place at the 1-position of the pyrazole ring only. In the case of thio-derivatives of pyrazolo[3,4-d]pyrimidines, S-alkylation occurs in addition to N-alkylation.

An important feature of the chemistry of dimethylformamide (DMF) acetals is N-, S-, and O-alkylation, which has been well-reviewed [1]. The N-alkylation of azoles by DMF acetals has received much less attention. We have previously reported the N-ethylation of cyanoaminopyrazoles by DMF diethyl acetal (I) or triethyl orthoformate (II) [2, 3]. A report has recently appeared on the N-methylation of benzimidazoles, 3-nitropyrrolo[2,3-b]pyridine, and 3-nitro-1,2,4-triazole with DMF dimethyl acetal, which was shown to be preferable to methylation with dimethyl sulfate or iodomethane [4]. It was therefore of interest to examine further the alkylating abilities of orthoacid derivatives.

We here describe the N-alkylation of some pyrazoles containing electron-acceptor or electron-donor substituents, in addition to previously-synthesized pyrazolo[-3,4-d]pyrimidines [5,6] by the acetal (I) and the orthoester (II). Heating 3-methoxycarbonylpyrazole (III) in acetal (I) in the absence of a solvent gives N-1- and N-2-ethyl-3-methoxycarbonylpyrazoles (IV) and (V), in yields of 41 and 36%, respectively. Treatment of the pyrazole (III) with the orthoester (II) under similar conditions did not result in N-alkylation, but in the presence of catalytic amounts of toluene-p-sulfonic acid compounds (IV) and (V) were obtained in yields of 38 and 23%, respectively. Attempts to alkylate 3-methylpyrazole with (I) or (II) under similar or more severe conditions were unsuccessful. Reaction of 3-cyano-4-methylmercaptopyrazolo[3,4-d]pyrimidine (VI) with (I) afforded 1-ethyl-3-cyano-4-methylmercaptopyrazolo[3,4-d]pyrimidine (IX), isolated by preparative chromatography on silica gel in 60% yield. This compound (IX) was also obtained in 43% yield by heating the pyrazolopyrimidine (VI) at 145°C with an excess of (II). On heating 3-cyano-4,6-dimethylmercaptopyrazolo[3,4-d]pyrimidine (VII) in (I) for 4 h at 80°C, there was obtained a 16% yield of 1-ethyl-3-cyano-4,6-dimethylmercaptopyrazolo[3,4-d]pyrimidine (X), most of the heterocycle (VII) failing to react. Under more severe conditions (120°C), both N-alkylation of the pyrazole ring and replacement of the 4-methylmercapto group by ethoxy occurred to give 55% of 1-ethyl-3-cyano-4-ethoxy-6-methylmercaptopyrazolo[3,4-d]pyrimidine (XI), no (X) being formed. Reaction of 3-cyano-4,6-dimethylmercaptopyrazolo[3,4-d]pyrimidine (VIII) with (I) resulted in both N- and S-alkylation, to give 1-ethyl-3-cyano-4,6-diethylmercaptopyrazolo[3,4-d]pyrimidine (XII) in 55% yield. It was not found possible to carry out N- or S-alkylation selectively. Compounds (VII) and (VIII) were not alkylated by the orthoester (II) even in the presence of toluene-p-sulfonic acid. (See scheme on following page.)

The structures of the products were confirmed by IR, UV, and PMR spectroscopy, and by elemental analysis. The IR spectra of all the products showed the absence of absorption at 3150-3300 cm^{-1} corresponding to stretching vibrations of the NH group, which is present in the starting heterocycles. In (IX-XII), absorption was seen at 2235-2245 cm^{-1} for valence

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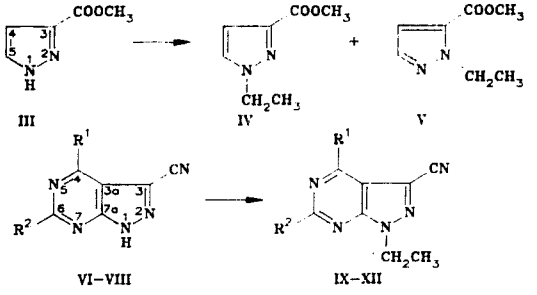
TABLE 1. ^{13}C NMR Spectral Data for (III-V) in $CDCl_3$ Solution

Compound	Chemical shift, δ, ppm (J_{CH}, Hz)						
	C=O [$^3J_{C,H(OCH_3)}$]	C-3 ($^2J_{C,H^1}$, $^3J_{C,H^5}$)	C-5 [$^1J_{C,H}$, $^2J_{C,H^4}$, $^3J_{C,H(CH_2)}$]	C-4 ($^1J_{C,H}$, $^2J_{C,H^5}$)	OCH_3 ($^1J_{C,H}$)	CH_2 [$^1J_{C,H}$, $^2J_{C,H(CH_3)}$]	CH_3 [$^1J_{C,H}$, $^2J_{C,H(CH_2)}$]
III	162,96 $J^3=3,9$	142,44 $J^2=7,4$ $J^3=5,5$	131,21 $J^1=189,2$ $J^2=8,3$	107,51 $J^1=180,8$ $J^2=9,0$	51,74 $J^1=147,4$	—	—
IV	162,66 $J^3=3,9$	143,00 $J^2=8,6$ $J^3=4,2$	129,51 $J^1=187,5$ $J^2=8,8$ $J^3=2,8$	108,75 $J^1=180,7$ $J^2=8,6$	51,60 $J^1=147,4$	47,66 $J^1=140,2$ $J^2=4,4$	15,23 $J^1=128,1$ $J^2=3,3$
V	159,72 $J^3=4,2$	131,31 M*	137,85 $J^1=187,5$ $J^2=5,0$	111,32 $J^1=179,8$ $J^2=10,5$	51,67 $J^1=147,4$	46,88 $J^1=141,3$ $J^2=4,4$	15,52 $J^1=128,1$ $J^2=3,6$
Δδ (IV−III)		0,56	−1,70	1,24			
Δδ (V−III)		−11,13	6,64	3,81			

*M is a complex multiplet.



VI, IX $R^1=SCH_3$, $R^2=H$; VII, X $R^1=R^2=SCH_3$; XI $R^1=OCH_2CH_3$, $R^2=SCH_3$; VIII $R^1=R^2=SH$; XII $R^1=R^2=SCH_2CH_3$

stretching of the nitrile group. Information on the site of introduction of the N-ethyl group into (IX-XII) was provided by the similarity of the UV spectra of these compounds to those of the previously-obtained 1-ribosides [5, 6]. The spectra of (X-XII) show characteristic absorption maxima at 248-254 and 290-294 nm, as in the corresponding 1-ribosides [5]. Compound (IX), like 3-cyano-4-methylmercaptopyrazolo[3,4-d]pyrimidine 1-riboside, gives two maxima at 302 and 312 nm, sharply differing in this respect from the 2-riboside [6].

There have been several literature reports of the greater resistance of the 6-methylmercapto group to nucleophilic replacement as compared with the 4-methylmercapto group in 4,6-disubstituted pyrazolo[3,4-d]pyrimidines [7, 8], suggesting that in (XI) the methylmercapto group in the 4- rather than the 6-position had been replaced by ethoxy.

The site of introduction of the ethyl group into the heterocycle in the isomeric pyrazoles (IV) and (V) was established by ^{13}C NMR spectroscopy. Complete assignment of the signals for all the carbon atoms in the spectra of these compounds, as well as in the starting N-unsubstituted heterocycle (III), was carried out taking into account the differences in the intensities of the signals when the spectra were obtained with full suppression of coupling of the protons with the carbon atoms, the nature of the fine structure of the signals, and the coupling constants when coupling of protons with carbon atoms was retained, and also with selective decoupling from protons (Table 1). The signal at lowest field in the spectrum of (III) was that for the carbonyl carbon, which experiences maximum deshielding by the electronegative oxygen atoms to which it is attached. This signal is seen as a quartet as a result of coupling with the OCH_3 protons. Towards higher field, signals for $C_{(3)}$ and $C_{(5)}$

are seen at 142.44 and 131.21 ppm, each with one neighboring nitrogen atom. A choice between these two signals may be made both from the greater relative intensity of the signal for $C(_5)$, and from their coupling constants and multiplicity. The signal at 107.51 ppm is attributed to $C(_4)$ on the basis of its chemical shift, high intensity (comparable to that of $C(_5)$), its $J_{C,H}^1$ value of 180.8 Hz, and the type of splitting (a doublet of doublets). The assignment of the signals for $C(_4)$ and $C(_5)$ was also confirmed by selective suppression of coupling of the carbon nuclei with protons $H(_4)$ and $H(_5)$. The signal for the OCH_3 carbon was seen at 51.74 ppm. Assignments of the signals for the carbons in (IV) and (V) were made similarly, from the changes in the chemical shifts and the fine structure of the signals for the carbon atoms of the pyrazole ring depending on the position of the substituent at nitrogen. The signals for the carbons of the ethyl group were seen at high field.

Examination of the spectral data shows that introduction of the ethyl group in (IV) as compared with (III) results in a shift of the $C(_5)$ signal to higher field by 1.70 ppm, whereas the $C(_3)$ and $C(_4)$ signals experience low-field shifts of 0.56 and 1.24 ppm, respectively. In the spectrum of (V), the signal for $C(_3)$ is shifted to higher field than in that of (III), by 11.13 ppm, the signals for $C(_4)$ and $C(_5)$ being shifted to lower field by 3.81 and 6.64 ppm.

It is known [9] that the introduction of a substituent at nitrogen in nitrogen heterocycles results in a shift in the ^{13}C NMR signal for the carbon atom adjacent to the nitrogen bearing the substituent to higher field than in the N-unsubstituted heterocycle (the α-shift). The signals for the β-carbons atom shifted usually to lower field (the β-shift). The nature of the shifts of the signals for $C(_3)$, $C(_4)$, and $C(_5)$ in the spectra of (IV) and (V) relative to the positions in the spectrum of the N-unsubstituted heterocycle (III) enables the structure of (IV) to be assigned on the basis of these considerations to the N-1-isomer, (V) being regarded as the 2-isomer.

The same conclusion may by drawn from a consideration of the fine structure of the signals for $C(_5)$ in (IV) and $C(_3)$ in (V), which contain N-ethyl substituents, as compared with the multiplicity of these signals in the spectrum of the original heterocycle (III). In the spectrum of (IV) obtained without suppression of coupling of the carbon atoms with protons, in contrast to the spectrum of (III) each of the doublet-of-doublets components of the signal for $C(_5)$ is further split into triplets as a result of coupling of the $C(_5)$ atoms and the methylene protons of the $N(_1)$-ethyl group with a $J^3_{C,H(CH_2)}$ value of 2.8 Hz. The multiplicity of the signal for $C(_3)$ (a doublet of doublets) here remains unchanged. In the spectrum of (V), also obtained with retention of coupling of protons with carbon atoms, in contrast to (IV) the signal for $C(_3)$ changes its multiplicity as compared with the starting compounds (III), whereas the multiplicity of the signal for $C(_5)$ remains unchanged. The signal for $C(_3)$ in the spectrum of (V) assumes a highly complex multiplet structure as a result of further coupling with protons $H(_4)$ and $H(_5)$ and the methylene protons of the $N(_2)$-ethyl group, in contrast to the doublet structure of the signal for this atom in (III), which bears no ethyl group. It was difficult to measure the coupling constant for $C(_3)$ in (V) as a result of its low intensity. These findings also show unambiguously that (IV) and (V) are the $N(_1)$- and $N(_2)$-ethyl derivatives of the pyrazole (III), respectively.

Comparison of the changes in the chemical shifts of the signals for $C(_3)$ and $C(_5)$ in (III) with those for the N-alkyl isomers (IV) and (V) enables the contributions of the separate $N(_{1H})$- and $N(_{2H})$-prototropic tautomers of (III) in $CDCl_3$ to be calculated using the equation $N(_{1H}) = (\delta_{III} - \delta_V)/(\delta_{IV} - \delta_V)$, where $N(_{1H})$ is the molar proportion of tautometer $N(_{1H})$, δ_i the chemical shift of $C(_3)$ (or $C(_5)$) in the spectra of (III-V). This calculation showed that in the pyrazole (III) the $N(_{1H})$-tautomer predominates, its molar proportion being 0.95 (0.8 when the calculation is carried out for the signals for $C(_5)$).

The acetal (I) is therefore a more effective alkylating agent than the orthoester (II). Alkylation by orthoacid derivatives evidently occurs only when they are protonated, so that it is normally carried out in the presence of acidic catalysts [10, 11]. The source of protons for the orthoesters may be acid added to the reaction mixture, but in the case of amide acetals acid catalysis is inapplicable as a result of the danger of hydrolysis thereof. The alkylating activity of DMF acetals is therefore shown only in those heterocycles which are capable of behaving as weak NH acids. The inability of the acetal (I) to alkylate 3-methylpyrazole appears to be due to the insufficient acidity of this heterocycle as compared with 3-methoxycarbonylpyrazole (III). It will be of interest to further examine the relationship between NH acidity in the heterocycles and its ability to undergo N-alkylation on treatment with amide acetals of varying types.

EXPERIMENTAL

IR spectra were obtained on a Perkin-Elmer 283 in KBr disks, and UV spectra on a Unicam SP-800 recording spectrophotometer in ethanol. ^1H NMR and ^{13}C NMR spectra were obtained for 1% (^1H) and 10% (^{13}C) solutions of the compounds in $CDCl_3$ on a Bruker WH-90, operating frequencies 90 (^1H) and 22.62 (^{13}C) MHz at 40°C, internal standards TMS (^1H, δ = 0.00 ppm) and $CDCl_3$ (^{13}C, δ = 77.00 ppm), the precision of measurement of the chemical shifts and coupling constants in the ^{13}C NMR spectra, due to numerical resolution, being 0.02 ppm and 0.5 Hz respectively; the power of the decoupling equipment in experiments with selective decoupling of the spin–spin interactions of the protons with carbons was $\gamma H_2/2\pi$ = 400 Hz. Analytical TLC was carried out on Siluful UV-254 plates in the system chloroform (A) and chloroform–methanol 99:1 (B), and preparative chromatography on plates (20 × 20 cm) with an unbound layer of LDL 5/40 silica gel (Czech SSR) of thickness 1.5 mm, using the same solvent systems unless otherwise indicated.

1-Ethyl-2-methoxycarbonylpyrazole (IV) and 2-Ethyl-3-methoxycarbonylpyrazole (V). A. A mixture of 1.2 g (9.5 mmole) of 3-methoxycarbonylpyrazole (III) and 4 ml of the acetal (I) was heated for 2 h at 140°C. The resulting solution was evaporated, the residue twice evaporated with 5 ml portions of toluene, and the residue subjected to chromatography on silica gel to give two zones with R_f 0.70 and 0.57 in system B, each zone then being subjected to further chromatographic purification using the same solvent system to give 0.60 g (41%) of (IV) and 0.52 g (36%) of (V).

Compound (IV): R_f 0.57 (B); UV spectrum, λ_{max} (log ε): 221 nm (3.81); ^1H NMR spectrum: 7.43 (1H, d, $J_{5,4}$ = 2.4 Hz, 5-H); 6.81 (1H, d, $J_{4,5}$ = 2.4 Hz, 4-H); 4.26 (2H, q, CH_2); 3.92 (3H, s, OCH_3); 1.52 ppm (3H, t, CH_3). Found, %: C 50.5; H 6.6; N 17.6. $C_7H_0N_2O_2 \cdot 0.75H_2O$. Calculated, %: C 50.3; H 6.9; N 16.9.

Compound (V): R_f 0.70 (B); UV spectrum: λ_{max} (log ε): 225 nm (3.84); ^1H NMR spectrum: 7.47 (1H, d, $J_{5,4}$ = 2.0 Hz, 5-H); 6.82 (1H, d, $J_{4,5}$ = 2.0 Hz, 4-H); 4.61 (2H, q, CH_2); 3.88 (3H, s, OCH_3); 1.44 ppm (3H, t, CH_3). Found, %: C 52.4; H 6.6. $C_7H_{10}N_2O_2 \cdot 0.25H_2O$. Calculated, %: C 52.8; H 6.7.

B. A mixture of 200 mg (1.6 mmole) of (III) and 20 mg (0.12 mmole) of toluene-p-sulfonic acid in 2 ml of the orthoester (II) was heated for 5 h at 140-150°C. Workup of the reaction mixture as in A above gave 75 mg (38%) of (IV) and 45 mg (23%) of (V), identical with those described above.

1-Ethyl-3-cyano-4-methylmercaptopyrazolo[3,4-d]pyrimidine (IX). A. A mixture of 0.32 g (1.7 mmole) of (VI) and 3 ml of the acetal (I) was heated for 6 h at 120°C, evaporated, the residue twice evaporated with 5 ml portions of toluene, and the residue subjected to preparative chromatography on silica gel in the system chloroform–methanol (95:5) to give (IX). An analytically pure sample was obtained by recrystallization from methanol. Yield 0.22 g (60%), mp 124-125°C, R_f 0.57 (B). IR spectrum: 2246 cm^{-1} (C≡N). UV spectrum, λ_{max} (log ε): 302 (4.15), 312 nm (4.07). ^1H NMR spectrum: 8.76 (1H, s, H-6); 4.56 (2H, q, CH_2); 2.75 (3H, s, SCH_3); 1.56 ppm (3H, t, CH_3). Found, %: C 49.6; H 4.5; N 31.5. $C_9H_9N_5S$. Calculated, %: C 49.4; H 4.2; N 31.9%.

B. A mixture of 100 mg (0.52 mmole) of (VI) and 1.5 ml of the orthoester (II) was heated for 7 h at 140-150°C. Workup as in method A gave 50 mg (43%) of (IX), identical with the material described above.

1-Ethyl-3-cyano-4,6-dimethylmercaptopyrazolo[3,4-d]pyrimidine (X). A mixture of 0.28 g (1.2 mmole) of (VII) and 3 ml of the acetal (I) was heated for 4 h at 80°C, evaporated, and the residue subjected to preparative chromatography in system A to give 0.05 g (16%) of (X) and 0.18 g of starting (VII).

Compound (X): mp 127-128°C, R_f 0.59 (A). IR spectrum: 2238 cm^{-1} (C≡N). UV spectrum, λ_{max} (log ε): 254 (4.47), 293 (4.16), 316 nm (3.95). ^1H NMR spectrum: 4.47 (q, CH_2); 2.71 and 2.63 (both s, $2SCH_3$); 1.53 ppm (t, CH_3). Found, %: C 44.9; H 4.2; N 26.6; S 24.5. $C_{10}H_{11}N_5S_2$. Calculated, %: C 45.4; H 4.2; N 26.5; S 24.3.

1-Ethyl-3-cyano-4-ethoxy-6-methylmercaptopyrazolo[3,4-d]pyrimidine (XI). A mixture of 0.68 g (2.9 mmole) of (VII) and 5 ml of acetal (I) was heated for 4 h at 120°C, the solution evaporated, and the residue twice evaporated with 5 ml portions of toluene. The residue was applied to a column of silica gel (2 × 30 cm), eluted with system B, and the fractions containing (XI) were combined, evaporated, and the residue recrystallized from methanol to

give 0.42 g (55%) of (XI); mp 94-95°C, R_f 0.50 (B). IR spectrum: 2242 cm^{-1} (C≡N). UV spectrum, λ_{max} (log ε): 248 (4.49), 290 nm (3.96). ^1H NMR spectrum: 4.65 and 4.47 (both q, OCH_2 and NCH_2); 2.61 (s, SCH_3); 1.52 and 1.49 ppm (both t, $2CH_3$). Found, %: C 50.4; H 5.3. $C_{11}H_{13}N_5OS$. Calculated, %: C 50.3; H 5.0.

1-Ethyl-3-cyano-4,6-diethylmercaptopyrazolo[3,4-d]pyrimidine (XII). A mixture of 0.30 g (1.4 mmole) of (VIII) and 2 ml of acetal (I) was heated for 4 h at 100°C and 3 h at 130°C. Separation was carried out as for (XI), the (XII) being eluted from the column with chloroform to give the pyrimidine (XII) as a yellow oil which crystallized from methanol. Yield 0.23 g (55%), mp 52-54°C, R_f 0.45 (B). IR spectrum: 2237 cm^{-1} (C≡N). UV spectrum, λ_{max} (log ε): 254 (4.45), 294 (4.15), 316 nm (3.92). ^1H NMR spectrum: 4.46, 3.37, and 3.22 (all q, $3CH_2$); 1.52, 1.45, and 1.43 ppm (all t, $3CH_3$). Found, %: C 48.6; H 5.2; N 24.3; S 21.9. $C_{12}H_{15}N_5S_2$. Calculated, %: C 49.2; H 5.2; N 23.9; S 21.9.

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