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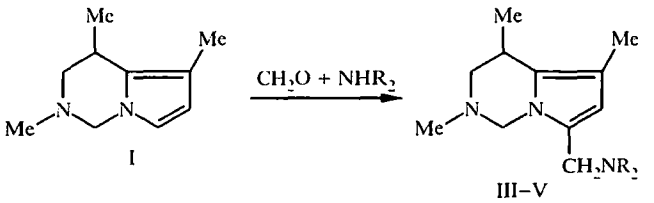
7-DIALKYLAMINOMETHYL-2,4,5-TRIMETYL- AND 2,4,5-TRIMETHYL-7-PHENYLIMINOMETHYL-1,2,3,4-TETRAHYDROPYRROLO[1,2-*c*]PYRIMIDINES

A. V. Varlamov, T. N. Borisova, E. A. Sorokina, A. I. Chernyshev, and A. N. Levov

The Mannich aminoalkylation of 2,4,5-trimethyl-1,2,3,4-tetrahydropyrrolo[1,2-c]pyrimidine and condensation of its 7-formyl derivative with aniline have been studied. 7-Morpholinomethyl- and 7-(N-methylpiperazinylmethyl)-substituted derivatives have been isolated. 7-Dimethylaminomethyl- and 7-phenyliminomethyl-substituted derivatives of tetrahydropyrrolo[1,2-c]pyrimidines are easily cleaved in the process of chromatographic isolation.

The formylation of 2,4,5-trimethyl-1,2,3,4-tetrahydropyrrolo[1,2-*c*]pyrimidine (I) occurs at the α-position of the pyrrole fragment, but the resulting 7-formyl derivative reacts with hydroxylamine and depending on the conditions the reaction leads to the corresponding oxime or to 4-methyl-5-(α-methylaminoethyl)-2-oximinomethylpyrrole, the product of cleavage of the amine fragment of compound (I) [1].

On continuation of studies on the reactivity of tetrahydropyrrolo[1,2-*c*]pyrimidine with the aim of introducing a pharmacophoric group, and also obtaining promising synthons, we have carried out the aminomethylation of compound I and condensation of its 7-formyl-substituted derivative II with aniline. Dimethylamine, N-methylpiperazine, and morpholine were used as amine component in the Mannich aminomethylation of compound I. In all cases aminomethylation occurred at the α-position of the pyrrole fragment (position 7).



III $R_2 = CH_2CH_2OCH_2CH_2$; IV $R_2 = CH_2CH_2N(CH_3)CH_2CH_2$; V R = Me

2,4,5-Trimethyl-7-morpholino-1,2,3,4-tetrahydropyrrolo[1,2-*c*]pyrimidine (III) was formed in 40% yield on aminomethylation of compound I with morpholine at 20°C. An acid catalyst was required when aminomethylating with N-methylpiperazine. The yield of the 7-(N-methylpiperazinyl)methyl-substituted derivative at -5 to -6°C was 54%, but at 20°C it was 14%. In the latter case di(N-methylpiperazinyl)methane, the condensation product of formaldehyde with N-methylpiperazine, was also formed. We were unable to isolate the product of dimethylaminomethylation of compound I. According to TLC data the aminomethylation product V is formed in reaction both with dimethylamine hydrochloride and formalin and with 8% dimethylamine solution in alcohol and formalin in the presence of acetic acid. However on separation of the reaction mixtures only the 7-formyl

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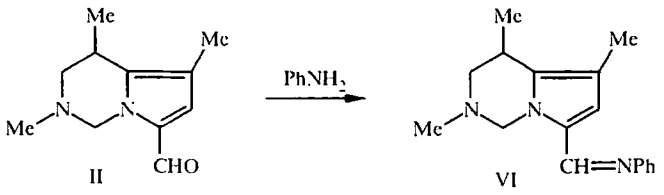
derivative of tetrahydropyrrolo[1,2-c]pyrimidine II and di(2,4,5-trimethyl-1,2,3,4-tetrahydropyrrolo-[1,2-c]-7-pyrimidinyl)methane [2] were obtained. According to chromato-mass spectrometry the same compounds were formed on reacting compound I with formalin. On aminomethylation of compound I with aminal – di(N,N-dimethylamino)methane in boiling dioxane [3] the aminomethylation product (~70%) and the formyl derivative II (30%) were formed according to ^{1}H NMR spectral data (see Table 1). However on chromatographic separation of the reaction mixture only the compounds I and II were isolated. Analogous case has been described in [4].

The preparation of 2,4,5-trimethyl-7-phenyliminomethyl-1,2,3,4-tetrahydropyrrolo[1,2-c]pyrimidine (VI) was effected by condensing compound II with aniline in the presence of glacial acetic acid. The reaction was conducted with azeotropic distillation of water. According to TLC data the condensation proceeded quantitatively, however it was not possible to isolate the individual compound VI. On chromatographing the reaction mixture on column with aluminum oxide or on silica gel the compound VI was decomposed into the 7-formyl derivative II and aniline. Compound VI also decomposed on standing in solvents.

Analysis of the reaction mixture with the aid of chromato-mass spectrometry and ^{1}H NMR spectroscopy (Table 1) unequivocally confirmed the formation of imino derivative VI.



II VI

Condensation of compound II with ethanolamine, benzylamine, *p*-anisidine, and 2-aminopyridine was unsuccessful under these conditions. It is interesting that the isomer of compound II at the ring junction, *viz.* 2-formyl-4,5,7-trimethyl-4,5,6,7-tetrahydropyrrolo[3,2-c]pyridine, under the same conditions forms condensation product with ethanolamine in 92% yield [5]. The high reactivity of the formyl group in the latter compound is probably caused by the possibility of forming hydrogen bond with the pyrrole NH proton.

The structures of compounds III-VI were confirmed unequivocally using ^{1}H NMR spectroscopy (see Table 1) by comparison with the spectra of the initial tetrahydropyrrolopyrimidine I and its formyl derivative II [1]. In the spectra of all the compounds doublet signals of AB system were observed from the two protons of the aminal group 1-CH_2 with geminal coupling constant equal to 9.5-11.3 Hz. A long range coupling constant $^4J_{1e3e}$ = 0.9 Hz was observed in the spectrum of compound III. This constant is not resolved for compounds IV and V and appears as additional peak broadening for the multiplet signals of protons 1-H_e and 3-H_e in comparison with the components of the 1-H_a and 3-H_a signals. The protons of the CH_2 group of the dialkylaminomethyl fragment are magnetically nonequivalent and appear as an AB system at 3.21-3.38 ppm with ^2J = 13.4-13.7 Hz. The presence of a twin set of signals for the protons of the tetrahydropyrrolopyrimidine fragment (except for the 6-H proton) in the spectra of compounds III-V indicates the existence of these compounds as a mixture of isomers at ratios of 5:1, 3:1, and 2:1 respectively. It may be suggested that these isomers arise due to disposition of the methyl group at $C_{(4)}$.

EXPERIMENTAL

^{1}H NMR spectra of 2% solutions of the synthesized compounds in $CDCl_3$ were recorded on a Bruker WH 400 spectrometer at 20°C. Chemical shifts were measured relative to TMS as internal standard. Mass spectra were obtained on MX 1303 and Kratos MS 25 RF instruments with direct insertion of samples into the ion source at ionizing voltage of 70 eV. Column chromatography was carried out on Al_2O_3 of Brockmann activity grade II. Thin-layer chromatography was carried out using plates with a bound layer of Alufol type Al_2O_3 and the solvent system ethyl acetate–hexane, 1:1.

TABLE 1. ^{1}H NMR Spectral Characteristics of Tetrahydropyrrolo-pyrimidines III-VI

Compound	Chemical shifts, δ, ppm, multiplicity (coupling constant, J, Hz)				
	1-H_a	1-H_e	2-CH_3	3-H_a	3-H_e
III (max/min)* (5: 1)	4.56 d (10.1) 5.03 d (11.3)	4.43 d (10.1; 0.9) 4.69 d (11.3; 0.9)	2.43 s 2.45 s	2.55 dd (12.2; 6.4) 2.61 dd (12.2; 5.6)	2.79 ddd (12.2; 5.8; 0.9) 2.79 ddd (12.2; 5.8; 0.9)
IV (max/min)* (3 : 1)	4.52 d (10.1) 5.04 d (11.3)	4.39 d*^{2} (10.1) 4.67 d*^{2} (11.3)	2.41 s 2.41 s	2.53 dd (12.8; 6.7) 2.58 dd (12.2; 6.7)	2.77 dd*^{2} (12.2; 5.8) 2.77 dd*^{2} (12.2; 5.8)
V (max/min)* (2 : 1)	4.53 d (9.8) 4.42 d (9.5)	4.31 d*^{2} (9.8) 4.13 d*^{2} (9.5)	2.42 s 2.40 s	—*^{3} —	—*^{3} —
VI*^{1}	5.20 d (11.3)	4.85 d (11.3)	2.48 s	2.61 dd (11.9; 5.5)	2.83 dd (11.9; 6.0)

Compound	4-H	4-CH_3	5-CH_3	6-H	7-R
III (max/min)* (5:1)	3.09 m 3.09 m	1.26 d (6.7) 1.31 d (6.7)	2.03 s 2.07 s	5.79 s 5.79 s	3.38 d; 3.29 d (7-CH_2, 13.4); 2.37 m [(CH_2)N]; 3.68 m [(CH_2)O]
IV (max/min)* (3:1)	3.07 m 3.07 m	1.25d (7.0) 1.30d (7.0)	2.01 s 2.05 s	5.77 s 5.77 s	3.38 d; 3.27 d (7-CH_2, 13.4); 2.25 s (N–CH_3); 2.20-2.53 $(CH_2)_4$
V (max/min)* (2:1)	—*^{3} —	—*^{3} —	2.03 s 2.00 s	5.78 s 5.78 s	3.30 d; 3.21 d (7-CH_2, 13.7); 2.16 s [$N(CH_3)_2$]
VI*^{1}	3.16 m	1.32 d (6.7)	2.08 s	6.46 s	8.13 s (CH=); 7.11 *o*-H; 7.15 *p*-H; 7.24 *m*-H

* Ratio of isomers.

*^{2} Broadened signals.

*^{3} Mixtures of compounds II and V, II and VI were analyzed, no assignment was made due to mutual overlap of signals.

2,4,5-Trimethyl-7-morpholino-1,2,3,4-tetrahydropyrrolo[1,2-*c*]pyrimidine (III). Compound I (0.4 g, 2.4 mmol) in ethanol (5 ml) was added dropwise to solution of morpholine (0.22 g, 2.5 mmol) and 37% formalin (0.23 g, 2.5 mmol) in ethanol (15 ml) at 0°C and the mixture was left for 3 h at 20°C. Alcohol was evaporated in vacuum, water (5 ml) was added, and the mixture extracted with ether (3 × 15 ml). The extract was dried over magnesium sulfate. The residue was chromatographed on column (1 × 32 cm), eluent hexane–ethyl acetate, 10:1. Compound III (0.26 g, 40%) was obtained as a yellow oil, R_f 0.7. Found, %: C 68.7; H 9.8; N 16.2. M^+ 263. $C_{15}H_{25}N_3O$. Calculated, %: C 68.4; H 9.5; N 16.0. M 263.

2,4,5-Trimethyl-7-(N-methylpiperazinylmethyl)-1,2,3,4-tetrahydropyrrolo[1,2-*c*]pyrimidine (IV). A. Compound I (0.33 g, 2 mmol) in ethanol (5 ml) was added to solution of N-methylpiperazine (0.2 g, 2 mmol), 37% formalin (0.18 g, 2 mmol), and glacial acetic acid (2 drops) in ethanol (15 ml) at 0°C. The reaction mixture was left

at 0 to -5°C for 3 h. Alcohol was distilled off in vacuum, water (15 ml) added, and the mixture extracted with ether (3 × 15 ml). The extract was dried over magnesium sulfate. After distilling off ether the residue was chromatographed on column (1 × 35 cm), eluent was hexane–ethyl acetate, 10:1. Compound IV (0.29 g, 54%) was obtained as a yellow oil; R_f 0.6. Found, %: C 69.3; H 11.0; N 20.4. M^+ 276. $C_{17}H_{16}N_4$. Calculated, %: C 69.6; H 10.1; N 20.3. M 276.

B. The residue obtained by the procedure described above from N-methylpiperazine (0.16 g, 1.6 mmol), 37% formalin (0.15 g, 1.6 mmol), and compound I (0.26 g, 1.6 mmol) in ethanol (20 ml) in the presence of glacial acetic acid (2 drops) but at 20°C, was chromatographed on column (1.5 × 16 cm) using hexane as eluent. Compound IV (56 mg, 14%) and di(N-methylpiperazinyl)methane (30 mg, 9%) were eluted sequentially. ^{1}H NMR spectrum: 2.25 (6H, s, N-CH_3); 2.45 (16H, m, N-CH_2); 2.63, 2.47 ppm (2H, dd, NCH_2N). Found: M^+ 212. $C_{11}H_{24}N_4$. Calculated: M 212.

Dimethylaminomethylation of Compound (I). A. Compound I (0.24 g, 1.5 mmol) and N,N,N',N'-tetramethylmethylenediamine (0.15 g, 1.5 mmol) in absolute dioxane (10 ml) were boiled for 7 h (check by TLC). The mixture was evaporated in vacuum, and the residue extracted with ether. The extract was dried over magnesium sulfate, and ether distilled off. The residue (0.19 g) contained compound II and the dimethylaminomethylation product V according to ^{1}H NMR spectra. The residue was chromatographed on a column (1.5 × 20 cm) using ethyl acetate–hexane, 1:7 as eluent. Compound I (50 mg, 20%) and 7-formyl derivative II (80 mg, 28%) were isolated.

B. Mixture of compound I (0.3 g, 1.8 mmol), dimethylamine hydrochloride (0.29 g, 3.6 mmol), and 37% formalin (0.33 g, 3.6 mmol) was boiled in alcohol (10 ml) (check by TLC). After evaporating alcohol, water (10 ml) was added to the residue, the mixture was extracted with ether, and the extract dried over magnesium sulfate. After evaporating ether, the residue (0.25 g) was chromatographed on column (1 × 20 cm), eluent ethyl acetate–hexane, 1:7. Formyl derivative II (22 mg, 7%) and di(2,4,5-trimethyl-1,2,3,4-tetrahydropyrrolo[1,2-*c*]-7-pyrimidinyl)methane (30 mg: 10%) were isolated as white needle-shaped crystals; mp 140-142°C (decomp., from hexane). A mixing test with standard sample [2] gave no depression of melting point.

2,4,5-Trimethyl-7-(N-phenyl)iminomethyl-1,2,3,4-tetrahydropyrrolo[1,2-*c*]pyrimidine (VI). Mixture of formyl derivative II (0.7 g, 4 mmol), aniline (0.74 g, 8 mmol), and glacial acetic acid (2 drops) in absolute toluene (30 ml) was boiled with a Dean and Stark head for 6 h (check by TLC). After distilling off toluene, the residual dark viscous oil contained, according to chromato-mass spectrometry, compound VI (M^+ 267) and the initial compound II (M^+ 192). This mixture was analyzed by ^{1}H NMR spectroscopy (see Table 1). It contained 40% of compound VI and 60% of initial compound II. The mixture was chromatographed on column (2.5 × 20 cm), eluent ethyl acetate–hexane, 1:10. The initial compound II (0.2 g, 30%) and aniline (0.3 g) were isolated.

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