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Azines and Azoles:
CXXI.[1] Alkylation of 5,7-Dihydro-4*H*-pyrano[2,3-*d*:6,5-*d*']-dipyrimidine-4,6(3*H*)-dione and Its 5-Phenyl Derivative

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Abstract—Methylation of 5,7-dihydro-4*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-4,6(3*H*)-dione and its 5-phenyl analog with dimethyl sulfate in the presence of LiOH in aqueous solution gives rise to the corresponding 3,7-dimethyl derivatives. The same isomers are formed by methylation of 5-phenyl-5,7-dihydro-4*H*-pyrano-[2,3-*d*:6,5-*d*']dipyrimidine-4,6(3*H*)-dione with methyl iodide in the presence of K_2CO_3 in *N,N*-dimethylacetamide. However, with ethyl bromide, propyl iodide, or butyl bromide instead of methyl iodide, mixtures of 3,7- and 1,7-dialkyl-5-phenyl-5,7-dihydro-4*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-4,6-diones were obtained.

Tricyclic systems containing a pyrimidine ring exhibit antimicrobial and antiviral activity *in vitro* [2, 3]. However, a more detailed study of the biological activity of this compounds is prevented by their poor solubility in water and most organic solvents. One of the ways to enhance the solubility is to introduce hydrophilic or hydrophobic functional groups, such as saccharide residues and their acyclic analogs, or hydrocarbon radicals. Enhanced lipophilicity can facilitate membrane transport and strengthen functional activity.

5,7-Dihydro-4*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-4,6(3*H*)-dione (**Ia**) and its 5-phenyl analog (**Ib**) are polyfunctional heterocyclic systems with several nucleophilic reaction centers. Therefore, their alkylation can give rise to various N- and O- and mono- and disubstituted products, depending on the method used.

Previously we showed [4] that pyranodipyrimidines **Ia** and **Ib** slowly react with a large excess of diazomethane to give a mixture of *O,O*-, *N,N*-, and *O,N*-dimethyl derivatives. Methylation of dilithium salts of compounds **Ia** and **Ib** (obtained by dissolving the **II** and **IIIa** in ~50% yields. The same reaction with sodium salts of **Ia** and **Ib** resulted in lower yields of dimethyl derivatives **II** and **IIIa**. These compounds are not O-methylation products, since they are hydrolytically stable. The IR spectra of the products contain a band at 1667 cm^{-1}, characteristic of carbonyl absorption, while the ^1H NMR spectra lack signals near δ 4 ppm, characteristic of methoxy groups.

According to the ^1H NMR spectra of compounds **II** and **IIIa**, the two methyl groups locate symmetrically at pyrimidine nitrogens. Their single singlet is observed at δ 3.30–3.40 ppm. The spectra lack NH proton signal at δ 12.5 ppm, characteristic of starting compounds **Ia** and **Ib**. The protons at C^2 and C^8, too, give a common singlet shifted downfield (δ 8.30–8.42 ppm) compared to the respective signal of pyridines **Ia** and **Ib** (δ 8.04 ppm). The aromatic and C^5H proton signals of compound **IIIa** appear at δ 7.12–7.27 and 4.95 ppm, respectively. In the spectrum of compound **II**, the C^5H_2 singlet overlaps with the CH_3 signal.

However, the spectra data give no unambiguous evidence for the positions of the methyl groups in compounds **II** and **IIIa**. Rigorous structural assessment can be derived from X-ray diffraction data and, indirectly, from quantum-chemical calculations.

Theoretically, *N,N*-dimethylpyranodipyrimidines **II** and **IIIa** can have three positional isomers **A**–**C**. Symmetrical location of the methyl group is only possible in structures **A** and **B**. In view of the aforesaid, we should decide between these two structures. Such choice can be based on their heats of formation calculated by the semiempirical PM3 method (GAMESS [5]) for molecules in a vacuum at 0 K (see table).

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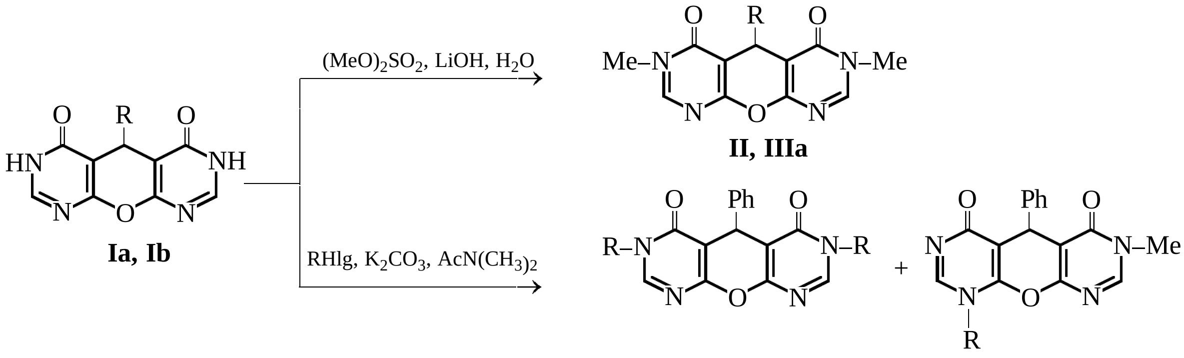
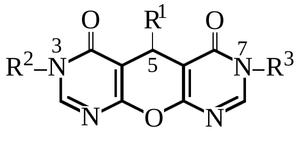
[1] For communication CXX, see [1].

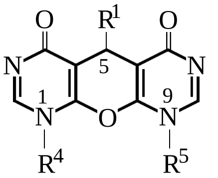


Hlg = Cl, Br, I; **I**, R = H (**a**), Ph (**b**); **II**, R = H; **III, IV**, R = Me (**a**), Et (**b**), Pr (**c**), Bu (**d**).

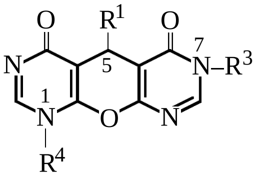
The calculations give preference to isomers with 3- and 7-methyl groups (structure **A**). The heats of formation of isomers with 1- and 9-methyl groups (structure **B**) are ~75 kJ mol^{-1} lower. Evidence for this conclusion comes from the similarity of the IR spectra of compounds **II** and **IIIa** to the spectrum of 6-methoxy-3-methylpyrimidin-4(3*H*)-one [6] which can be considered as a model of structure **A**.



A



B



C

We were the first to alkylate pyranodipyrimidines **Ia** and **Ib** with C$_1$–C$_4$ alkyl halides at 1 : 2–2.5 pyranodipyrimidine : alkyl halide ratios in an aprotic dipolar solvent (*N*,*N*-dimethylacetamide) in the presence of potassium carbonate at 60–70°C. The time of each reaction was determined chromatographically.

The methylation of pyranodipyrimidine **Ib** with methyl iodide under the above conditions for 24 h gave only one of the possible isomer (TLC data). The R_f values and proton chemical shifts for this compound were identical with those for compound **IIIa** prepared by methylation of compound **Ib** with dimethyl sulfate. In this connection the compound obtained was assigned the structure of 3,7-dimethyl derivative **IIIa**.

High yields (60–70%) were attained in alkylations of pyranodipyrimidine **Ib** with ethyl and butyl bromides, as well as propyl iodide. The reaction times were 20–24 h.

Unlike the reaction with methyl iodide, the latter reactions always provided, according to TLC and ^{1}H NMR data, mixtures of two *N*,*N*-dialkyl derivatives **III** and **IV**. Therewith, the alkyl groups in one of the isomers located symmetrically and in the other, unsymmetrically. We suggested that, like with dimethyl derivatives **II** and **IIIa**, the alkyl groups in the symmetrical isomers are in the 3 and 7 positions (structure **A**). The unsymmetrical isomers are inevitably 1,7-dialkyl derivatives (structure **C**). The calculated heats of formation of these isomers show that structure **A** is, on the one hand, thermodynamically more favorable than stucture **C** (see table). On the other hand, the differences in the heats of formation [$\Delta\Delta_f H_0^0 = \Delta_f H_0^0(\mathbf{C}) - \Delta_f H_0^0(\mathbf{A})$] between the corresponding 1,7- and 3,7-dialkyl isomers, including dimethyl derivatives, are as small as ~33 kJ/mol, which is much smaller than the difference in the heats of formation [$\Delta\Delta_f H_0^0 = \Delta_f H_0^0(\mathbf{B}) - \Delta_f H_0^0(\mathbf{A}) \sim 75$ kJ mol^{-1}] between 1,9- and 3,7-dimethyl derivatives. At the same time, comparison of the heats of formation of various *N*,*N*-dialkylpyranodipyrimidines provides no explanation for the fact that dimethylation of compounds **Ia** and **Ib** results in exclusive formation of a single isomer, while the reactions with longer chain alkylating agents give rise to two isomers. Probably, the rate of methylation of pyranodipyrimidines **Ia** and **Ib** into the 3 and 7 positions is much higher than in the 1 position, whereas the other alkyls enter these positions at comparable rates.

We could separate some of the mixtures of isomers **III** and **IV** and isolate at least one isomer by fractional crystallization. Thus recrystallization from benzene gave chromatographically individual 3,7-diethylpyranodipyrimidine **IIIb**. Individual **IVb** was obtained by recrystallization of the mixture from hexane. By recrystallization from benzene we also managed to obtain individual 3,7-dipropylpyranodipyrimidine **IIIc** that is poorly soluble in this solvent. At the same time, the isolated 1,7-dipropylpyranodipyrimidine **IVc** contained a considerable admixture of isomer **IIIc**. The mixture of 3,7- and 1,7-dibutylpyranodipyrimidines **IIId** and **IVd** could not be separated by fractional crystallization, since the compounds were readily soluble in organic solvents. Thus, increasing alkyl chain length in compounds **III** and **IV** renders their mixtures more and more difficult to separate in view of the equalized lipophilic–hydrophylic properties of the two isomers.

The ^{1}H NMR spectra of 3,7-dialkyl derivatives **IIIb**–**IIId** and compound **IIIa** are very similar to each other. Principal distinctions are associated with the different alkyl groups. Thus the CH_3 proton signals form triplets at δ 0.8–1.2 ppm, whereas the CH_2 proton signals form multiplets at δ 3.6–3.9 (NCH_2), 1.5–1.7 ($NCH_2C\mathit{H}_2$), and 1.2–1.3 ppm ($NCH_2CH_2 \cdot C\mathit{H}_2$).

The ^{1}H NMR spectra of 1,7-dialkyl derivatives **IVb**–**IVd** exhibit the following features indicative of an unsymmetrical structure of these molecules. The C^2H and C^8H proton signals form two singlets at δ 8.4–8.5 ppm, whereas the NCH_2 protons, rather than forming one multiplet, like in isomers **IIIb**–**IIId**, appear as two multiplets at δ 4.2–4.3 (2H, N^1CH_2) and 3.6–3.9 ppm (2H, N^7CH_2). Furthermore, the C^5H proton singlet in the spectrum of compounds **IV** is shifted downfield by ~0.1 ppm compared with the respective signals of compounds **III**; in the spectra of isomeric mixtures, these signals are well resolved.

Unlike 5-phenylpyranodipyrimidine (**Ib**), pyranodipyrimidine **Ia** much slower reacts with alkyl halides. Small amounts of *N*,*N*-dialkylpyranodipyrimidines are detected in 72 h only, but the isolable yields of the products are no higher than 5–7%. Most pyranodipyrimidine **Ia** remains unreacted. Spectral and chromatographic analyses reveal formation in this case of a mixture of disubstituted isomers as amorphous substances with close Rf values; individual products could not be isolated by repeated precipitation from methylene chloride with hexane. The unsuccessful alkylation of pyranodipyrimidine **Ia** is probably explained by the fact that this compound is extremely poorly soluble even in high-polarity aprotic solvents (dimethylacetamide, DMF, DMSO).

Heats of formation ($\Delta_f H^0_0$, kJ mol^{-1}) of *N*,*N*-dialkyldihydro-4*H*-pyrano-[2,3-*d*:6,5-*d*']dipyrimidine-4,6(3*H*)-diones **II, IIIa**–**IIId**, and **IVb**–**IVd** in a vacuum at 0 K (PM3 calculation)

Comp. no.	R^1	R^2	R^3	R^4	R^5	$-\Delta_f H^0_0$
II	H	Me	Me	–	–	233.84
		–	–	Me	Me	159.39
		–	Me	Me	–	200.99
IIIa	Ph	Me	Me	–	–	98.34
		–	–	Me	Me	21.96
		–	Me	Me	–	64.78
IIIb	Ph	Et	Et	–	–	147.74
IVb	Ph	–	Et	Et	–	115.94
IIIc	Ph	Pr	Pr	–	–	192.61
IVc	Ph	–	Pr	Pr	–	160.85
IIId	Ph	Bu	Bu	–	–	238.08
IVd	Ph	–	Bu	Bu	–	206.36

Attempted alkylation of pyranodipyrimidines **Ia** and **Ib** with [2-(bromomethoxy)ethyl] acetate failed. Chromatography revealed only traces of new compounds even after very long reaction times.

Thus, the reaction of 5-phenylpyranodipyrimidine **Ib** with alkyl halides in *N*,*N*-dimethylacetamide in the presence of K_2CO_3 gives rise to dialkyl-substituted pyranodipyrimidines, either as individual compounds or isomeric mixtures which can not infrequently be separated to isolate analytically pure substances. Unlike 5-phenylpyranodipyrimidine **Ib**, its unsubstituted analog pyranodipyrimidine **Ia** is much harder alkylated and form a difficultly separable mixture of dialkyl-substituted pyranodipyrimidines in low yields.

EXPERIMENTAL

The IR spectra in KBr were measured on an FSM-1201 Fourier IR spectrometer. The electronic absorption spectra in methanol were obtained on an SF-56 spectrophotometer. The ^{1}H NMR spectra in DMSO-d_6 were taken on Bruker AM-200 (200 MHz) and Bruker AM-500 (500 MHz) spectrometers. Product purity and reaction progress were controlled TLC on Silufol UV-254 plates, development in UV light or iodine vapor. The melting (decomposition) points were measured in capillaries and were not corrected. The solvents and reagents were purified by known procedures [7].

3,7-Dimethyl-5,7-dihydro-4*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-4,6(3*H*)-dione (II). Aqueous LiOH, 4 mmol, was added to a suspension of 1 mmol of pyranodipyrimidine **Ia** in 5 ml of water. The precipitate was let to dissolve, and 2 mmol of dimethyl sulfate was added, maintaining the pH of the solution at 10–11 with aqueous LiOH. After the reaction was complete (within 30 min), the precipitate that formed was filtered off and washed with water to obtain colorless crystals poorly soluble in organic solvents. Yield 52%, mp 247–249°C, R_f 0.54 (eluent 5% NH_4Cl). 1H NMR spectrum, δ, ppm: 3.30 br.s (8H, C^5H_2, NCH_3), 8.30 s (2H, $C^{2,8}H$). Found N, %: 22.51. $C_{11}H_{10}N_4O_3$. Calculated N, %: 22.77.

3,7-Dimethyl-5-phenyl-5,7-dihydro-4*H*-pyrano-[2,3-*d*:6,5-*d*']dipyrimidine-4,6(3*H*)-dione (IIIa). *a*. The synthesis was performed similarly to the above-described using 3.4 mmol of phenylpyranodipyrimidine **Ib**, 13.6 mmol of LiOH, and 19.6 mmol of dimethyl sulfate. Reaction time 1.5 h. Yield 52%, colorless crystals, mp >300°C, R_f 0.43 (eluent chloroform–methanol, 10 : 1). IR spectrum, ν, cm^{-1}: 440, 485, 595, 725, 760, 830, 880, 1015, 1060, 1135, 1215, 1245, 1345, 1400, 1430, 1500, 1575, 1600, 1675, 1880, 2445, 2950, 3050, 3110, 3490. UV spectrum, λ_{max}, nm: 275 sh. ^1H NMR spectrum, δ, ppm: 3.37 s (6H, CH_3), 4.95 s (1H, C^5H), 7.12–7.27 m (5H, Ar–H), 8.41 s (2H, $C^{2,8}H$). Found N, %: 17.01. $C_{17}H_{15}N_4O_3$. Calculated N, %: 17.34.

b. Phenylpyranodipyrimidine **Ib**, 2 mmol, was dissolved in 10 ml of warm *N,N*-dimethylacetamide, and the solution was cooled. Potassium carbonate, 3 mmol, and a solution of 6 mmol of methyl iodide in 10 ml of *N,N*-dimethylacetamide were added, and the mixture was stirred at 40°C until reaction completion (by TLC) and then concentrated to ~1/3 the initial volume at reduced pressure (25–30 mm Hg). To a stirred residue, cold water was added to form a thick material that gradually crystallized. The crystals were filtered off, washed with cold water, dried, and recrystallized from methylene chloride–hexane. Yield 63%. The sample has the same physicochemical and spectral characteristics as that obtained by procedure *a*.

3,7-Diethyl-5-phenyl-5,7-dihydro-4*H*-pyrano-[2,3-*d* : 6,5- *d*']dipyrimidine-4,6(3*H*)-dione (IIIb) and 1,7-diethyl-5-phenyl-5,7-dihydro-4*H*-pyrano-[2,3-*d*:6,5-*d*']dipyrimidine-4,6(3*H*)-dione (IVb) were prepared similarly to compound **IIIa** (procedure *b*). Alkylating agent ethyl bromide. A few KI crystals were added to the reaction mixture. According to TLC data, a mixture of two compounds was obtained, yield 70%, mp 230–240°C. The mixture was subjected to fractional crystallization from benzene from which compound **IIIb** crystallized, yield 49%, mp 280–284°C, R_f 0.40 (eluent chloroform–methanol, 25 : 1). UV spectrum, λ_{max}, nm: 274 sh. ^1H NMR spectrum, δ, ppm: 1.22 t (6H, CH_3), 3.78–3.94 m (4H, CH_2), 4.98 s (1H, C^5H), 7.13–7.24 m (5H, Ar–H), 8.44 s (2H, $C^{2,8}H$). Found N, %: 5.38. $C_{19}H_{19}N_4O_3$. Calculated N, %: 15.95. Compound **IVb** was precipitated from the benzene mother liquor, yield 26%, mp 175–180°C, Rf 0.32 (eluent eluent chloroform–methanol, 25 : 1). UV spectrum, λ_{max}, nm: 275 sh. ^1H NMR spectrum, δ, ppm: 1.24 m (6H, CH_3), 3.81–3.98 m (2H, N^7CH_2), 4.29–4.39 m (2H, N^1CH_2), 5.07 s (H, C^5H), 7.21 m (5H, Ar–H), 8.43 s (1H, C^8H), 8.48 s (1H, C^2H).

3,7-Dipropyl-5-phenyl-5,7-dihydro-4*H*-pyrano-[2,3-*d*:6,5-*d*']dipyrimidine-4,6(3*H*)-dione (IIIc) and 1,7-propyl-5-phenyl-5,7-dihydro-4*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-4,6(3*H*)-dione (IVc) were synthesized similarly to compound **IIIa** (procedure *b*). Alkylating agent propyl iodide. According to TLC data, a mixture of two compounds was obtained, yield 60%, mp 147–155°C. The mixture was subjected to fractional crystallization from benzene from which compound **IIIc** crystallized, yield 30%, mp 198–203°C, R_f 0.40 (eluent chloroform–methanol, 25 : 1). UV spectrum, λ_{max}, nm: 275 sh. ^1H NMR spectrum, δ, ppm: 0.85 t (6H, CH_3), 1.56–1.67 m (4H, CH_2CH_3), 3.66–3.93 m (4H, NCH_2), 4.97 s (1H, C^5H), 7.17–7.23 m (5H, Ar–H), 8.43 s (2H, $C^{2,8}H$). Found N, %: 14.52. $C_{21}H_{23}N_4O_3$. Calculated N, %: 14.78. Compound **IVc** was precipitated from the benzene mother liquor with hexane; after double reprecipitation it contained a considerable admixture of compound **IIIc**; yield 57%, mp 130–135°C, R_f 0.50 (eluent chloroform–methanol, 25 : 1). UV spectrum, λ_{max}, nm: 275 sh. ^1H NMR spectrum, δ, ppm: 0.78–0.88 m (6H, CH_3), 1.57–1.66 m (4H, CH_2CH_3), 3.66–3.94 m (2H, N^7CH_2), 4.23–4.27 m (2H, N^1CH_2), 5.06 s (1H, C^5H), 7.17–7.34 m (5H, Ar–H), 8.42 s (1H, C^8H), 8.45 s (1H, C^2H). Found N, %: 14.56. $C_{21}H_{23}N_4O_3$. Calculated N, %: 14.78.

3,7-Dibutyl-5-phenyl-5,7-dihydro-4*H*-pyrano-[2,3-*d*:6,5-*d*']dipyrimidine-4,6(3*H*)-dione (IIId) and 1,7-dibutyl-5-phenyl-5,7-dihydro-4*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-4,6(3*H*)-dione (IVd) were synthesized similarly to compound **IIIa** (procedure *b*). Alkylating agent butyl bromide. According to TLC data, a mixture of two compounds was obtained, yield 62%, mp 72–80°C. The mixture was subjected to fractional crystallization from benzene–hexane to isolate 0.57 g (41%) of a substance melting at 104–106°C. By ^1H NMR data, it was a roughly equimolar mixture of isomers **IIId** and **IVd**. Compound **IIId**, R_f 0.76 (eluent chloroform–methanol, 25 : 1). ^{1}H NMR spectrum, δ, ppm: 0.85–0.92 m (6H, CH_3), 1.20–1.28 m (4H, CH_2CH_3), 1.53–1.59 m (4H, NCH_2CH_2), 3.68–3.90 m (4H, NCH_2), 4.96 s (1H, C^5H), 7.20 m (5H, Ar–H), 8.47 s (2H, $C^{2,8}H$). Compound **IVd**, R_f 0.81 (eluent chloroform–methanol, 25 : 1). ^{1}H NMR spectrum, δ, ppm: 0.85–0.92 m (6H, CH_3), 1.20–1.28 m (4H, CH_2CH_3), 1.53–1.59 m (4H, NCH_2CH_2), 3.68–3.90 m (2H, N^7CH_2), 4.27–4.30 m (2H, N^1CH_2), 5.03 s (1H, C^5H), 7.20 m (5H, Ar–H), 8.48 m (2H, $C^{2,8}H$). Found N, %: 13.56. $C_{23}H_{27}N_4O_3$. Calculated N, %: 13.76.

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