PYRIMIDINES

LXVII.* FORMYLPYRIMIDINE N-OXIDE DERIVATIVES

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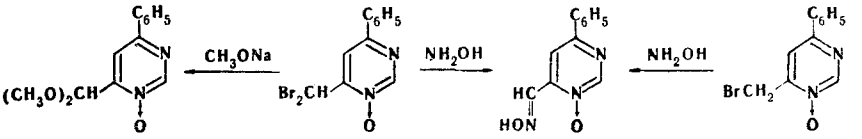
The preparation of dimethylacetals and oximes of 2(6)-formyl-4-phenylpyrimidine N-oxides from the corresponding bromomethyl derivatives is described. A syn configuration was assumed for the oximes from the PMR spectra.

Studies devoted to the synthesis of derivatives of formylpyridines and N-oxides and quaternary salts of pyridine, among which physiologically active compounds are found [2-5], are promoting the development of research in this direction [6, 7]. However, very little data on aldehydes and their derivatives in the pyrimidine series are available [8-10], and no data are available for derivatives of pyrimidine N-oxides. On the basis of a study of the possibility of the use of pyrimidine N-oxides for the synthesis of substituted pyrimidines and the literature data on the successful preparation of aldehyde derivatives in the purine N-oxide series [11] we investigated the possibility of the synthesis of some derivatives of formylpyrimidine N-oxides on the basis of halodimethylpyrimidine N-oxides.

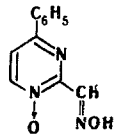
We used 2(6)-mono and 2(6)-dibromomethyl-4-phenylpyrimidine 1-oxides, which were previously obtained by bromination of the corresponding methylphenylpyrimidine N-oxides [1], as the starting compounds.

6-Dibromomethyl-4-phenylpyrimidine 1-oxide (I) reacted quite rapidly with sodium methoxide at room temperature to give a compound in which the N→O group ($\nu_{N\to O}$ 1255 cm^{-1}) is retained, according to the IR spectral data; the IR spectrum also contains absorption bands at 2835 and 1075 cm^{-1}, which are characteristic for acetals [12] and are absent in the spectrum of the starting compound.

In addition to the signals of aromatic protons (7.98 and 7.43 ppm, 5H), the PMR spectrum of the product contains signals at 3.53 (6H) and 5.83 ppm (1H), which can be assigned to the acetal group (CH_3O and $CH(OCH_3)_2$, respectively [13]), and signals of H^2 and H^5 protons at 8.94 and 7.90 ppm. On the basis of these data it may be assumed that the isolated compound is 6-formyl-4-phenylpyrimidine 1-oxide dimethylacetal (II). The latter readily forms a 2,4-dinitrophenylhydrazone.



II I III IV



VI

A compound corresponding to the expected 6-formyl-4-phenylpyrimidine 1-oxide oxime (III), according to the analytical and spectral characteristics, was obtained by the action of hydroxylamine on oxide I. Thus the PMR spectrum of this compound contains proton signals at 8.57 and 12.72 ppm (each 1H), which were absent in the spectrum of starting I and should

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be assigned to the protons of an oximinomethyl group (CH=NOH). However, the yield of III was very low, and it was difficult to purify. Since oximes can also be obtained from monohalomethyl derivatives by treatment with excess hydroxylamine [14], we also used this method and obtained oxime III in 80% yield from 6-bromomethyl-4-phenylpyrimidine 1-oxide (IV). The same method was used to obtain 2-formyl-4-phenylpyrimidine 1-oxide oxime (VI) in 65% yield from 2-bromomethyl-4-phenylpyrimidine 1-oxide (V).

The problem of the determination of the configuration is an important and interesting one for oximes. It was difficult to use IR spectroscopy to establish the configurations of oximes III and VI because of the low solubilities of these compounds. At the same time, the position of the signal of the proton of the OH group in the PMR spectra (12.72 ppm for III and 12.50 ppm for VI) also did not make it possible to choose unambiguously between the syn and anti forms [10]. To determine the configurations we used the principle found in the pyridine series [3], which is also valid for pyrimidine derivatives [15]. According to this principle, in the case of the syn isomers the signal of the α-H atom of the azine ring is shifted 0.3-0.5 ppm with respect to the CH=NOH group to stronger field as compared with the position of the signal of the CH=N– proton, whereas in the case of the anti isomers it is shifted to weaker field. The position of the signals of the H^5 (8.23 ppm) and CH=N (8.57 ppm) protons in III provides a basis for the assumption that this oxime has a syn configuration, i.e., the usual configuration for oximes [3]. Compound VI, which was obtained in the same way as oxime III, evidently also as a syn configuration. The oximes obtained in this research are stable compounds that are only slightly soluble in organic solvents and virtually insoluble in water.

EXPERIMENTAL

The IR spectra of KBr pellets or solutions of the compounds in chloroform were recorded with a UR-20 spectrometer. The UV spectra of the compounds were recorded with a Specord UV-vis spectrophotometer. The PMR spectra were recorded with a Varian A56/60 spectrometer with hexamethyldisiloxane as the internal standard; the chemical shifts are presented on the δ scale. The individuality of the compounds was verified by thin-layer chromatography (TLC) on Silufol UV-254.

6-Formyl-4-phenylpyrimidine 1-Oxide Dimethylacetal (II). A 0.5-g (1.5 mmole) sample of dibromo derivative I was added to a solution of 0.13 g of sodium in 10 ml of absolute methanol, and the mixture was stirred at room temperature for 10 min. It was then evaporated carefully in vacuo, and the residue was separated with a column filled with silica gel (elution with ethyl acetate) to give 0.1 g (26%) of dimethylacetal II. PMR spectrum ($CDCl_3$): 8.84 (1H, s, H^2), 7.98 (aromatic $2H_o$, d), 7.90 (1H, s, H^5), 7.43 (3H, aromatic $2H_m + H_p$), 5.83 1H, s, [$CH(OCH_3)_2$], and 3.53 ppm (6H, s, OCH_3).

6-Formyl-4-phenylpyrimidine 1-Oxide 2,4-Dinitrophenylhydrazone. This compound had mp 266-269°C (alcohol–acetic acid). Found: N 19.7%. $C_{17}H_{12}N_6O_5 \cdot C_2H_5OH$. Calculated: N 19.7%; M 380 (by mass spectrometry). $C_{17}H_{12}N_6O_5$. M 380.

6-Formyl-4-phenylpyrimidine 1-Oxide Oxime (III). A 20-ml sample of an aqueous methanol solution of hydroxylamine, obtained by neutralization of 1 g of hydroxylamine hydrochloride with a saturated solution of NaOH, was added to a warm solution of 0.3 (1.1 mmole) of IV in 50 ml of alcohol, and the mixture was allowed to stand in a dark place for 3 days. The resulting precipitate was removed by filtration to give oxime III, with mp 252-254°C (alcohol), in 80% yield. UV spectrum (in alcohol), λ_{max} (log ε): 204 (3.96), 222 (3.92), 290 (4.32), 363 nm (3.66). PMR spectrum (in DMSO): 12.72 (1H, s, NOH), 9.29 (1H, s, H^2), 8.57 (1H, s, CH=N), 8.23 (1H, s, H^5), 8.13 (2H, dd, aromatic H_o), and 7.57 ppm (3H, m, aromatic H). Found: C 61.7; H 4.47; N 19.4%. $C_{11}H_9N_3O_2$. Calculated: C 61.4; H 4.21; N 19.5%.

2-Formyl-4-phenylpyrimidine 1-Oxide Oxime (VI). This compound, with mp 247-249°C (alcohol), was similarly obtained in 65% yield. UV spectrum (in alcohol), λ_{max} (log ε): 204 (4.05), 256 (4.26), 317 nm (4.36). PMR spectrum (in DMSO); 12.50 (1H, s, NOH), 8.73 (1H, s, CH=N), 8.63 (1H, d, J = 3.4 Hz, H^6), 8.25 (1H, d, J = 3.4 Hz, H^5), 8.10 (2H, dd, aromatic H), and 7.57 ppm (3H, m, aromatic H). Found: N 19.1%. $C_{11}H_9N_3O_2$. Calculated: N 19.5%.

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ACTION OF NUCLEOPHILIC AGENTS ON THE PYRIMIDINE RING

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It is shown that 2-alkylpyrimidine methiodides in which the alkyl group is activated by electron-acceptor substituents undergo recyclization to the corresponding 2-methylaminopyridines in an alcohol solution of methylamine. Similar recyclization also takes place without quaternization of the pyrimidine ring when there is a strong electron-acceptor substituent (a nitro group) in the ring.

The pyrimidine ring is capable of adding the $\overline{N}H_2$ anion (potassium amide in liquid ammonia) to give a σ complex [1], while ammonia itself (as well as methylamine) requires heating (up to 190°C), during which the ring undergoes complete cleavage, and 2-methyl-5-ethylpyridine is formed from two molecules of pyrimidine [2]. Hydrazine hydrate, which is a strong nucleophile, also cleaves the pyrimidine ring to give pyrazole when the reaction mixture is heated to 130°C [3]. Even covalent addition of the elements of water, which may lead to hydrolytic opening of the pyrimidine ring [7], is known for pyrimidines, the ring of which is condensed with another aromatic ring or has a strong electron-acceptor substituent [4-6].

Pyrimidinium salts react with nucleophiles under mild conditions. In particular, the action of an alkaline agent leads to cleavage of the $N_{(1)}$–$C_{(6)}$ bond and solvolytic cleavage of the open form [8]. The open form sometimes closes again with the inclusion of a nucleophile molecule. Thus pyrimidine methiodide undergoes ring opening in liquid ammonia and recyclizes to give the nonalkylated pyrimidine. The scheme of this dealkylation through a step involving recyclization is confirmed by experiments with a labeled nitrogen atom [9], although this does not exclude the possibility of competitive direct dealkylation due to attack by the nucleophile on the methyl group. Instances of similar recyclizations in which the resulting ring includes a fragment of the attacking reagent [for example, the $\overline{C}H(CN)_2$ anion] are known [10, 11]. In addition to this, alkylpyrimidines and particularly their quaternary salts can react as CH acids under the influence of nucleophiles. Unstable anhydronium bases are formed from the quaternized structures in this case [7].

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