PYRIMIDINES

XVIII. Synthesis and Some Properties of Pyrimidine-2-aldehydes*

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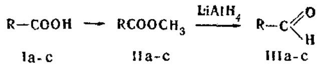
By the reduction of the corresponding esters with lithium aluminum hydride at −60 to −70° C, a number of pyrimidine-2-aldehydes have been obtained. It has been shown that the carbonyl groups in these aldehydes is highly reactive: they readily add alcohols and form hydrates.

Aldehydes of the pyrimidine series are a comparatively small and little-studied group of pyrimidine derivatives, the bulk of the main representatives being pyrimidine-4-aldehydes and -5-aldehydes. Pyrimidine-2-aldehydes have scarcely been studied at all. The formation of pyrimidine-2-aldehydes, usually isolated in the form of derivatives, has been reported in a few papers [2–6]. Free pyrimidine-2-aldehydes have not hitherto been obtained.

To prepare pyrimidine-2-aldehydes we selected the method of the low-temperature lithium aluminum hydride reduction of esters [7, 8]. This method ensures selective reduction, and the yield of aldehydes amounts to 50–60% (determined from the yield of 2,4-dinitrophenyl hydrazones).



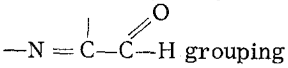
$$R{-}COOH \longrightarrow RCOOCH_3 \xrightarrow{LiAlH_4} R{-}C\overset{O}{\underset{H}{\lessgtr}}$$

Ia-c IIa-c IIIa-c

a R=pyrimid-2-yl
b R=4,6-dimethylpyrid-2-yl
c R=4,6-diphenylpyrid-2-yl

The pyrimidine carboxylic acids **Ia–Ic** were synthesized from the corresponding 2-chloropyrimidines by a known method [9, 10]. Methyl 4,6-diphenylpyrimidine-2-carboxylate (**IIc**) was obtained by the action of the acid chloride (prepared with thionyl chloride) on absolute methanol. The esters **IIa** and **IIb** were obtained in good yield by the esterification of the corresponding acids at 20–25° C with methanol saturated with HCl. The esters were reduced in absolute tetrahydrofuran solution at from −60 to −65° C. According to thin-layer chromatography, reduction generally gave a mixture of the unchanged ester, the aldehyde, and traces of the corresponding alcohol.

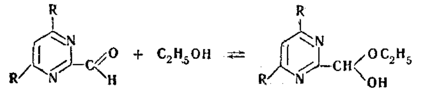
The pyrimidine-2-aldehydes **IIIa–IIIc** are unstable compounds rapidly darkening in the air. Pyrimidine-2-aldehyde (**IIIa**) is apparently converted into a hydrated form by adsorbing atmospheric moisture. The IR spectrum of **IIIc** taken in carbon tetrachloride has, in addition to an absorption band at 1745 cm^{-1} (C=C of an aldehyde) a strong broad band at 3450–3480 cm^{-1} (stretching vibrations of a bound OH group), which shows the partial hydration of the carbonyl group. The capacity for forming hydrates has been reported for other heterocyclic aldehydes containing a



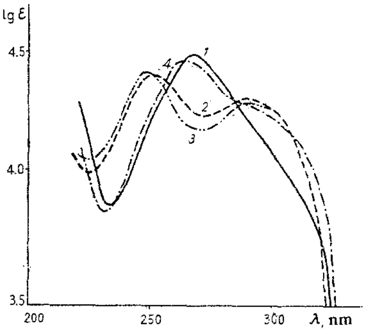
$$-N=\overset{|}{C}-\overset{O}{\overset{\|}{C}}-H$$

grouping [11, 12].

In ethanolic solutions of the pyrimidine-2-aldehydes an equilibrium between the aldehyde and its semiacetal is rapidly set up:



The UV spectra of **IIIc** taken in cyclohexane and in ethanol differ considerably because in ethanolic solution a reaction leading to a change in the chromophoric system takes place. The UV spectrum of **IIIc** in ethanol is similar to the UV spectrum of 2-hydroxymethyl-4,6-diphenlypyrimidine [13]. In the IR spectra of the pyrimidine-2-aldehydes taken in carbon tetrachloride with the addition of an equimolecular amount of ethanol, a decrease in the intensity of the band of the C=O group with time and the appearance of an OH group band is observed.



UV absorption spectra: 1) 4,6-diphenylpyrimidine-2-aldehyde (in cyclohexane); 2) 4,6-diphenylpyrimidine-2-aldehyde (in ethanol); 3) 2-hydroxmethyl-4,6-diphenylpyrimidine (in ethanol); 4) methyl 4,6-diphenylpyrimidine-2-carboxylate (in ethanol).

This ease of formation of hydrates and semiacetals shows the considerable reactivity of the carbonyl group in the pyrimidine-2-aldehydes, apparently because of the additional polarization of the C=O bond under the influence of the pyrimidine ring.

The pyrimidine-2-aldehydes readily form 2,4-dinitrophenylhydrazones and bisulfite derivatives. On reaction with malonic acid in pyridine, **IIIc** gives β-(4,6-diphenylpyrimid-2-yl)acrylic acid.

We propose subsequently to make a detailed study of the reactivity of the carbonyl group in the pyrimidine-2-aldehydes.

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*For part XVII, see [1]

Methyl 4,6-diphenylpyrimidine-2-carboxylate (IIc) [Performed by V. P. Krivopalov.] A suspension of 4 g of **Ic** in 40 ml of absolute benzene was treated with 3.5 ml of $SOCl_2$ and a few drops of dimethylformamide. The mixture was boiled with stirring for 1.5 hr. After cooling, the solvent and the excess of $SOCl_2$ were distilled off in vacuum. The dry residue of acid chloride was treated with 70 ml of absolute methanol. The solution was boiled for 2 hr, the excess of methanol, was distilled off, and the residue was treated with 5% $NaHCO_3$ solution. The precipitate was filtered off, washed with water, and dried to give 3.4 g (81%) of **IIc**, mp 135–137° C (from methanol). Found, %: C 74.7; H 4.95; N 9.61. Calculated for $C_{18}H_{14}N_2O_2$, %: C 74.5; H 4.86; N 9.65. IR spectrum: 1760 cm^{-1} (C=O in an ester).

4,6-Diphenylpyrimidine-2-aldehyde (IIIc). In a current of nitrogen, 30 ml of a 0.33 M solution of lithium aluminum hydride (0.38 g, 0.01 mole) in tetrahydrofuran was added over 30 min to a solution of 6.5 g (0.02 mole) of **IIc** in 70 ml of absolute tetrahydrofuran at from –65 to –70° C. After 15 min, 4 ml of acetic acid was added and the mixture was evaporated in vacuum (10–15° C). To the residue was added 50 ml of water, and concentrated HCl to bring the pH to 4. Then it was extracted with chloroform, the combined extracts were washed with aqueous sodium bicarbonate solution, and dried with calcined $MgSO_4$, and the solvent was evaporated off to give 3.78 g of solid product. The yield of **IIIc** was 58% (determined from the yield of 2,4-dinitrophenyl hydrazone). The aldehyde was purified via the bisulfite derivative; to a solution of the reduction product in chloroform was added an excess of a 40% solution of sodium bisulfite, and the mixture was stirred for 2 hr and left overnight, after which the precipitate was filtered off and was washed with ethanol and ether; the bisulfite derivative was hydrolyzed by heating with 30% K_2CO_3 solution in the water bath for 15–20 min. The precipitate of **IIIc** was filtered off and dried. Mp 126–128° C (from a mixture of petroleum ether and benzene). Found, %: C 78.28; H 4.74; N 10.56. Calculated for $C_{17}H_{12}N_2O$, %: C 78.46; H 4.61; N 10.77. IR spectrum: 1740 cm^{-1} (C=O in aldehydes). **2,4-Dinitrophenyl hydrazone:** mp 257–260° C (from ethyl acetate). Found, %: C 62.61; H 3.65; N 19.24. Calculated for $C_{23}H_{16}N_6O_4$, %: C 62.70; H 3.64; N 19.09.

β-(4,6-Diphenylpyrimid-2-yl)acrylic acid. A few drops of piperidine was added to a mixture of 0.67 g (2.6 mM) of **IIIc**, 0.6 g (8 mM) of malonic acid, and 6 ml of pyridine, and it was heated in the water bath for 3 hr. The cooled solution was poured into 50 ml of ice water and left overnight in the refrigerator. The precipitate was filtered off, washed with water, and dried, to give 0.45 g (57%) of the acid. Mp 230–232° C (from benzene). Found, %: C 75.69; H 4.67; N 9.38. Calculated for $C_{19}H_{14}N_2O_2$, %: C 75.50; H 4.65; N 9.27. IR spectrum: 1660 cm^{-1} (C=C); 1710 cm^{-1} (C=O in acids).

Methyl 4,6-dimethylpyrimidine-2-carboxylate (IIb). A solution of 16 g (0.1 mole) of **Ib** in 60 ml of absolute methanol saturated with HCl was kept at room temperature for two days. The methanol and the HCl were distilled off in vacuum, the residue was treated with ether, and the solution was neutralized with solid sodium bicarbonate. The ethereal solution was poured off from the solid matter and this was treated with ether several times more; the combined extracts were dried, the ether was evaporated off, and the residue was distilled in vacuum to give 9.3 g (62%) of product. Bp 122–123° C (7 mm), n_D^{20} 1.5089. IR spectrum: 1760 cm^{-1}. According to the literature [9], bp 142° C (11 mm).

4,6-Dimethylpyrimidine-2-aldehyde (IIIb). This was obtained in a similar manner to **IIIc** from 5 g (0.03 mole) of **IIb** and 0.57 g (0.01 mole) of lithium aluminum hydride. After the usual working up, 3.1 g of **IIIb** was obtained. Yield 52% (as the 2,4-dinitrophenyl hydrazone). The aldehyde was purified by recrystallization and subsequent vacuum sublimation. Mp 89–90° C (from petroleum ether). Found, %: C 61.16; H 5.90; N 20.51. Calculated for $C_7H_8N_2O$, %: C 61.67; H 5.88; N 20.59. IR spectrum: 1740 cm^{-1}. **2,4-Dinitrophenyl hydrazone:** mp 240–243° C (from benzene). Found, %: N 26.61. Calculated for $C_{13}H_{12}N_6O_4$, %: N 26.60.

Methyl pyrimidine-2-carboxylate (IIa). This was obtained in a similar manner to **IIb**. Yield 50%. Mp 103–104° C (from petroleum ether). According to the literature [13], mp 104–105° C.

Pyrimidine-2-aldehyde (IIIa). This was obtained from 1.8 g (0.013 mole) of **IIa** and 0.26 g (0.007 mole) of lithium aluminum hydride in a similar manner to that described for **IIIc**. The yield of **IIIa** was 50% (determined as the 2,4-dinitrophenyl hydrazone). Bp 78–82° C (9 mm). **2,4-Dinitrophenyl hydrazone:** mp 273–273.5° C (from ethyl acetate). Found, %: C 45.48; H 2.81: Calculated for $C_{11}H_8N_6O_4$, %: C 45.83; H 2.78.

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