1-TETRAHYDROFURANYL- AND 1-TETRAHYDROPYRANYL-SUBSTITUTED 3-HYDROXY-1,6-DIHYDROPYRIDAZIN-6-ONES

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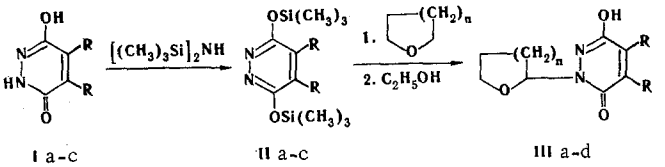
The reaction of 3,6-bis(trimethylsiloxy)pyridazine and its 4,5-dihalogen-substituted derivatives with 2-chlorotetrahydrofuran and 2-chlorotetrahydropyran has given 3-hydroxy-1-(tetrahydrofuranyl- and 3-hydroxy-1-(tetrahydropyranyl)-1,6-dihydropyridazin-6-ones, the structure of which as 1-substituted derivatives has been confirmed by an investigation of their IR spectra. On the basis of a study of ionization constants, the hypothesis has been put forward that these compounds exist in the hydroxy form.

The present work was devoted to the synthesis and investigations of analogs of the "nucleosides" of 3-hydroxy-1,6-dihydropyridazin-6-one (maleic acid hydrazide Ia), which differ from the corresponding ribosides of deoxyribosides [1] by the fact that in place of a monosaccharide residue they contain a tetrahydrofuran or a tetrahydropyran ring.

Our experiments showed that (Ia), unlike other 3- and 3,4- derivatives of 1,6-dihydropyridazin-6-one [2], does not react either with 2,3-dihydrofuran or with 2,3-dihydropyran, and therefore we studied the reaction of the 3,6-bis(trimethylsiloxy)pyridazines (IIa-c) with 2-chlorotetrahydrofuran and 2-chlorotetrahydropyran, and found that in a nonpolar solvent 1-tetrahydrofuranyl- and 1-tetrahydropyranyl-3-trimethylsiloxy-1,6-dihydropyridazin-6-ones are formed, the subsequent hydrolysis of which gives the 3-hydroxy-1-(tetrahydrofuranyl)- and 3-hydroxy-1-(tetrahydropyranyl)dihydropyridazinones (IIIa-d) with a yield of about 40-50% (Table 1).

The C–N glycosidic bond in (IIIa-c) proved to be less stable than in the corresponding pyrimidine derivative [3], and therefore the reaction with 2-chlorotetrahydrofuran and the subsequent solvolysis had to be performed in the range of temperatures from –20 to –10°C. In the reaction of (IIa) with 2-chlorotetrahydropyran, it is possible to use higher temperatures – from 20 to 50°C – and to perform solvolysis at 20°C. Under these conditions, compounds (IIb) and (IIc) do not react with 2-chlorotetrahydropyran.

In the IR spectra of compounds (IIIa-d) absorption bands in the 1070-1085 and 1045-1050 cm^{-1} region are due to the –C–O–C–O stretching vibrations in the tetrahydrofuran and tetrahydropyran rings [4, 5].



I a-c II a-c III a-d

I-III a-d R = H; I-III b R = Cl; I-III c R = Br; III a-c n = 1; III d n = 2

The absorption band in the 1635-1670 cm^{-1} region corresponds to the characteristic vibrations of the C=O group of a pyridazinone ring, as has been shown for 1-methyl-3-hydroxy-1,6-dihydropyridazin-6-one (IV) [6]. In addition, the spectra lack an absorption band at 3150-3170 cm^{-1} corresponding to the vibrations of

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TABLE 1. 3-Hydroxy-1-(tetrahydrofuranyl)- and 3-Hydroxy-1-(tetrahydropyranyl)-1,6-dihydropyridazin-6-ones

Compound	mp, °C*	Empirical formula	Found, %			Calc., %			Yield, †, %
			C	H	N	C	H	N	
IIIa	146—147	$C_8H_{10}N_2O_3$	52,67	5,54	15,42	52,74	5,53	15,38	39
IIIb	135—136	$C_8H_8Cl_2N_2O_3$	36,91	3,40	10,69	36,94	3,10	10,77	40
IIIc	150—151	$C_8H_8Br_2N_2O_3$	28,11	2,34	8,09	28,26	2,37	8,24	51
IIId	163—164	$C_9H_{12}N_2O_3$	55,09	6,15	14,33	55,09	6,15	14,54	50

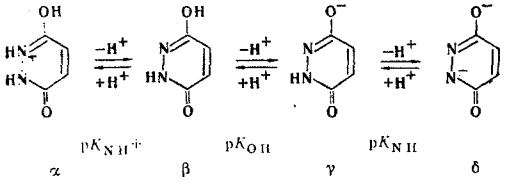
*For (IIIa-c) with decomposition. Compounds (IIIa-d) were recrystallized from ethyl acetate.
†Calculated on the (Ia-c).

TABLE 2. pK_{OH} Values for the 3-Hydroxy-1,6-dihydropyridazin-6-ones

Compound	pK_{OH}	Analytical wavelength, nm
IIIb	3,98±0,04	318
IIIc	4,14±0,02	321
IIIa	5,82±0,06	308
IIId	5,83±0,03	308
Ia[7, 9]	5,65±0,03	303
IV[8, 9]	5,62±0,03	303

an N−H bond. It must be mentioned that absorption in this region is characteristic for 1,6-dihydropyridazin-6-ones unsubstituted at N_1, including (Ia), as has been established by Sheinker et al. [6] and has been shown by us for compounds (Ib, c). This indicates that (IIIa-d) are N_1 derivatives. In these compounds (see [6]) a broad absorption band is observed in the 2500-2650 cm^{-1} region which apparently shows the presence of an intermolecular hydrogen bond arising between the carbonyl and the hydroxy groups.

In order to determine the possible lactim-lactam tautomeric forms, for (IIIa-d), we measured the ionization constants of these compounds in aqueous solution. The general scheme of the protolytic [7-9] equilibrium in aqueous solutions for 3-hydroxy-1,6-dihydropyridazin-6-ones includes the N_2 protonation of the cation (α), the molecular form (β), the anion (γ) formed by the ionization of these compounds at the O−H bond, and the dianion (δ) arising on ionization at the N_1−H bond.



It proved to be impossible to determine the pK_a values in strongly acid media for the compounds studied because of their instability. Table 2 gives the pK_a values for compounds (IIIa-d); since the latter are between 3.98 and 5.83, it may be considered that they relate to the dissociation of the hydroxy group (the β form) [9]. Consequently, it may be assumed that compounds (IIIa-d) exist in the hydroxy form. The increase in the acidity of (IIIb) and (IIIc) as compared with (IIIa) is apparently due to the electron-accepting influence of the substituents, but in this case the presence of a hydroxy group is not a matter of doubt.

An approximate evaluation of the pK values shows that the passage from the monoanion to the dianion takes place only at pH > 13, as has been shown more than once [7, 9] in the study of the structure of other 3-hydroxy derivatives of 1,6-dihydropyridazin-6-one.

EXPERIMENTAL

The IR spectra were obtained on a UR-20 instrument in the 900-1800 cm^{-1} region (NaCl prism) and the 2300-3200 cm^{-1} region (LiF prism) in paraffin oil and hexachlorobutadiene. In the pK_a determinations we used $1.4\text{-}2 \cdot 10^{-4}$ M aqueous solutions of (IIIa-d). Acetate buffer mixtures were used the pH values of which were determined on an LPU-01 pH meter calibrated with a hydrogen phthalate buffer solution. The

pK_a determinations were performed at a temperature of 20 ± 1°C. The UV spectra were obtained on a "Specord" instrument (GDR).

3-Hydroxy-1-(tetrahydrofuraryl)-1,6-dihydropyridazin-6-ones (IIIa). a) A mixture of 4.5 g (0.04 mole) of (Ia) [10], 20 ml of hexamethyldisilazane, and 2 ml of chlorotrimethylsilane was heated without the access of moisture at 160-170°C for 4 h, and then the excess of hexamethyldisilazane was distilled off under reduced pressure in a current of dry nitrogen at a bath temperature not exceeding 80°C. The residue of (IIa) was dissolved in 25 ml of dry benzene and, with stirring and cooling to −20°C, 2.7 ml (0.03 mole) of 2-chlorotetrahydrofuran [11] was added, the temperature was kept at −20 to −10°C for 8 h, and then the mixture was evaporated at 2-3 mm to a viscous syrup (all the operations were performed in a current of dry nitrogen) which was dissolved in 20 ml of ethyl acetate and, with stirring and cooling to −20°C, 2 ml of ethanol was added. The precipitate that deposited was rapidly filtered off and was washed twice with ethyl acetate. The filtrates were combined and evaporated under reduced pressure.

b) Compound (IIa) was obtained as in method a) but was distilled in vacuum. The yield of (IIa) was 8.1 g (79%), bp 88-90°C (2 mm), mp 60-62°C. The (IIa) was treated with 2-chlorotetrahydrofuran as in method a.

Compounds (IIIb) and (IIIc) were obtained in a similar manner to (IIIa) from (IIb) and (IIc), respectively.

4,5-Dichloro-3,6-bis(trimethylsiloxy)pyridazine (IIb). This was obtained similarly to (IIa) from 4.3 g (0.02 mole) of (Ib) [12], 13.6 ml of hexamethyldisilazane, and 1.36 ml of chlorotrimethylsilane. The yield of (IIb) was 6.65 g (86%), bp 112-113°C (3 mm), mp 55-56°C.

4,5-Dibromo-3,6-bis(trimethylsiloxy)pyridazine (IIc). This was obtained in a similar manner to (IIa) from 10.9 g (0.04 mole) of (Ic) [12], 20.1 ml of hexamethyldisilazane, and 2 ml of chlorotrimethylsilane. The yield of (IIc) was 13.1 g (78%), bp 125-127°C (2 mm), mp 71-72°C.

3-Hydroxy-1-(tetrahydropyranyl-1,6-dihydropyridazin-3-one (IIId). With stirring and cooling to 0°C, 4.3 ml (0.04 mole) of 2-chlorotetrahydropyran [13] was added to a benzene solution of (IIa) and the mixture was kept at 20°C for 2 h and at 40-50°C for 7 h. Then it was worked up as for (IIIa). Solvolysis was performed at 0°C, and then the temperature was raised to 20°C and the mixture was kept at this temperature for 30 min. The further working up was similar to that for (IIIa).

LITERATURE CITED

1. J. Pliml and F. Šorm, Coll., 30, 3744 (1965).
2. H. Kühmstedt and G. Wagner, Arch. Pharm., 301, 660 (1968).
3. S. A. Hiller, M. Yu. Lidak, R. A. Zhuk, A. É. Berzinya, K. Ya. Pets, I. N. Getsova, and É. I. Bruk, Khim. Geterotsikl. Soedin., 375 (1969).
4. R. Nahum, Ann. Chim., 3, 108 (1958).
5. N. Nagasawa, V. Kumshiro, and T. Takenishi, J. Org. Chem., 31, 2685 (1966).
6. Yu. N. Sheinker, T. V. Gortinskaya, and T. P. Sycheva, Zh. Fiz. Khim., 31, 600 (1957).
7. A. Albert and J. N. Philips, J. Chem. Soc., 1294 (1956).
8. D. M. Miller and R. W. White, Can. J. Chem., 34, 1510 (1956).
9. I. V. Turovskii, V. T. Glezer, L. Ya. Avota, Ya. P. Stradyn', and S. A. Hiller, Khim. Geterotsikl. Soedin., 993 (1973).
10. É. É. Dunkel' and S. A. Hiller, Izv. Akad. Nauk LatvSSR, 79, 105 (1954).
11. H. Gross, Ber., 95, 83 (1962).
12. J. Druey and K. Eichenberger, US Patent No. 2,792,195 (1957); Chem. Abstr., 51, 16567 c (1957).
13. M. Kratochvil, J. Jonas, O. Bartes, and H. Gross, Ber., 99, 1218 (1966).