2,3,5,8(1)-TETRAHYDROIMIDAZO[1,2-*a*]PYRIMIDINE-2,5-DIONE DERIVATIVES

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The corresponding ylidene, azomethine, and azo derivatives of 2,3,5,8(1)-tetrahydroimidazo[1,2-*a*]pyrimidine-2,5-dione were synthesized by reaction of 7-methyl- and 6-bromo-7-methyl-2,3,5,8(1)-tetrahydroimidazo[1,2-*a*]pyrimidine-2,5-diones with aldehydes, insatin, aromatic nitroso compounds, and arenediazonium salts. Ylidene derivatives of 7-methyl-2,3,5,8(1)-tetrahydroimidazo[1,2-*a*]pyrimidine-2,5-dione were also obtained by reaction of 2-amino-4-methyl-6-oxo-1,6-dihydro-1-pyrimidylacetic acid with carbonyl compounds.

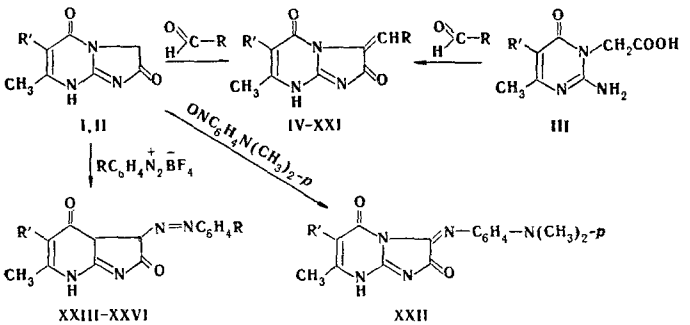
In order to search for biologically active compounds, we investigated the reactions of 2,3,5,8(1)-tetrahydroimidazo[1,2-*a*]pyrimidine-2,5-diones [1] with carbonyl compounds (aldehydes and isatin), nitroso compounds, and diazonium salts at the active methylene grouping located between the two electron-acceptor groups, just as was previously done for similar structures (for example, see [2]).

It was found that 7-methyl- and 6-bromo-7-methyl-2,3,5,8(1)-tetrahydroimidazo[1,2-*a*]pyrimidine-2,5-diones (I, II) readily react with aliphatic, aliphatic-aromatic, aromatic, and heterocyclic aldehydes, as well as isatin, on heating in ethanol in the presence of a catalyst (piperidine) or in glacial acetic acid in the presence of anhydrous sodium acetate to give ylidene derivatives (IV-XXI, Table 1).

Ylidene derivatives (VIII, XIII, XV, and XVI) were also obtained by reaction of 2-amino-4-methyl-6-oxo-1,6-dihydro-1-pyrimidylacetic acid (III) [1] with aldehydes (by heating in glacial acetic acid in the presence of anhydrous sodium acetate).

An azomethine derivative (XXII) was obtained by reaction of I with nitrosodimethylaniline in ethanol, while diazo coupling products (XXIII-XXVI) were formed with arenediazonium salts (best of all with arenediazonium tetrafluoroborates) in glacial acetic acid or water in the presence of an equimolecular amount of alkali.

The structures of IV-XXVI were confirmed by their IR spectra, which contain distinct absorption bands of CO and NH groups at 1640-1765 and 3080-3400 cm^{-1}, respectively.



A large number of the synthesized substances are inactive with respect to Gram-negative and Gram-positive microorganisms, and only V, XVI, XVIII, and XXIV suppress the growth of Staphyloccoccus aureus and Escherichia coli, Salmonella typhosa, and the dysentery bacillus in 1:2000 and 1:4000 cultures.

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TABLE 1. Ylidene (IV-XXI), Azomethine (XXII), and Azo Derivatives (XXIII-XXVI) of 2,3,5,8(1)-Tetrahydroimidazo[1,2-*a*]pyrimidine-2,5-dione

Compound	R	R'	mp, °C	Empirical formula	Found, %			Calc., %			Yield, %
					C	H	N	C	H	N	
IV	Citral residue	H	150—152	$C_{17}H_{21}N_3O_2$	67,8	6,7	14,3	68,2	7,0	14,1	90
V	$C_6H_4CH=CH$	H	>280	$C_{16}H_{13}N_3O_2 \cdot 0,5H_2O$	66,8	4,7	14,9	66,7	4,9	14,6	90
VI	*p*-$(CH_3)_2CHC_6H_4$	H	280—282	$C_{17}H_{17}N_3O_2$	69,3	6,1	14,2	69,1	5,8	14,2	83
VII	*o*-HOC_6H_4	H	262—264	$C_{14}H_{11}N_3O_3 \cdot 0,5H_2O$	60,0	4,3	15,2	60,4	4,4	15,1	56
VIII	*p*-HOC_6H_4	H	>280	$C_{14}H_{11}N_3O_3$	62,0	4,4	15,5	62,4	4,1	15,7	59—69
IX	*o*-$CH_3OC_6H_4$	H	>280	$C_{15}H_{13}N_3O_3 \cdot 0,5H_2O$	61,6	4,8	14,4	61,6	4,8	14,4	86
X	*p*-$CH_3OC_6H_4$	H	>280	$C_{15}H_{13}N_3O_3$	63,5	4,8	14,6	63,6	4,6	14,8	64
XI	*p*-BrC_6H_4	H	>300	$C_{14}H_{10}BrN_3O_2$ [a]	51,0	3,4	13,1	50,6	3,0	12,7	68
XII	2-HO—5-BrC_6H_3	H	>300	$C_{14}H_{10}BrN_3O_2 \cdot H_2O$ [b]	46,0	3,4	11,4	45,9	3,3	11,5	57
XIII	*p*-$(CH_3)_2NC_6H_4$	H	>300	$C_{16}H_{16}N_4O_2$	64,5	5,6	19,1	64,9	5,4	18,9	83—87
XIV	*p*-$(C_2H_5)_2NC_6H_4$	H	>300	$C_{18}H_{20}N_4O_2$	67,0	6,1	16,9	66,7	6,2	17,3	40
XV	*o*-$O_2NC_6H_4$	H	280—282	$C_{14}H_{10}N_4O_4$	56,4	3,0	18,9	56,4	3,3	18,8	43
XVI	*p*-$O_2NC_6H_4$	H	328—330	$C_{14}H_{10}N_4O_4 \cdot H_2O$	53,4	3,5	18,0	53,2	3,8	17,7	80—93
XVII	2-Furyl	H	>300	$C_{12}H_9N_3O_3$	59,2	4,1	17,5	59,3	3,7	17,3	81
XVIII	Citral residue	Br	210—212	$C_{17}H_{20}BrN_3O_2$ [c]	—	—	10,7	—	—	11,1	73
XIX	$C_6H_4CH=CH$	Br	>300	$C_{16}H_{12}BrN_3O_2$ [d]	53,6	3,3	11,4	53,6	3,4	11,7	83
XX	C_6H_5	Br	258—260	$C_{14}H_{10}BrN_3O_2$ [e]	50,8	3,3	13,1	50,6	3,0	12,7	96
XXI	Isatin residue	H	254—256	$C_{15}H_{10}N_4O_3$	60,7	3,5	—	61,2	3,4	—	30
XXII	*p*-$(CH_3)_2NC_6H_4N$	H	189—191	$C_{15}H_{15}N_5O_2$	60,4	5,0	—	60,0	5,1	—	40
XXIII	H, $C_6H_5N=N$	H	264—266	$C_{13}H_{11}N_5O_2$	58,2	4,1	26,3	58,(	4,1	26,1	30—98
XXIV	H, *p*-$CH_3OC_6H_4N=N$	H	>300	$C_{14}H_{13}N_5O_2$	56,0	4,5	23,7	56,5	4,4	23,4	63—99
XXV	H, *p*-$BrC_6H_4N=N$	H	>300	$C_{13}H_{10}BrN_5O_2$ [f]	44,9	3,0	20,4	44,8	2,9	20,1	46
XXVI	H, *p*-$H_2NSO_2C_6H_4N=N$	H	280—282	$C_{13}H_{12}N_6O_4S$ [g]	44,7	3,8	24,5	44,8	3,5	24,1	63—69

[a] Found: Br 23.5%. Calculated: Br 24.0%. [b] Found: Br 22.9%. Calculated: Br 23.0%. [c] Found: Br 20.8%. Calculated: Br 21.1%. [d] Found: Br 22.0%. Calculated: Br 22.3%. [e] Found: Br 23.9%. Calculated: Br 24.1%. [f] Found: Br 22.8%. Calculated: Br 23.0%. [g] Found: S 9.4%. Calculated: S 9.2%.

EXPERIMENTAL

Ylidene Derivatives of 2,3,5,8(1)-Tetrahydroimidazo[1,2-*a*]pyrimidine-2,5-diones (IV-XXI, Table 1). A) A 0.01-0.011-mole sample of the aldehyde and anhydrous sodium acetate (in amounts equal to the weight of I or II) were added to a solution of 0.01 mole of I or II in 10-15 ml of glacial acetic acid, and the mixture was refluxed for 1-3 h. It was then cooled, and 40-50 ml of water and a 20% solution of sodium hydroxide were added to pH 5-6. The resulting precipitate was removed by filtration and washed with water to give IV-XIV and XVI-XX.

B) A 1.47-g (0.01 mole) sample of isatin and two to three drops of piperidine were added to a suspension of 1.65 g (0.01 mole) of I in 60 ml of absolute ethanol, and the mixture was refluxed for 40 h. It was then cooled, and the precipitate was removed by filtration and washed successively with hot water and ethanol. The yield of XXI was 0.88 g (30%).

C) A 0.01-0.011-mole sample of the aldehyde was added to a mixture of 1.83 g (0.01 mole) of III and 1.83 g of anhydrous sodium acetate in 10-15 ml of glacial acetic acid, and the mixture was refluxed for 1-3 h and worked up as in experiment A. The yields of VIII, XIII, XV, and XVI were 59, 83, 43, and 80%, respectively.

Compounds VI, X, XI, XV, and XX were pale-yellow crystalline substances, IV, V, VII-IX, XII, and XVI-XIX were yellow crystalline substances, XIII and XIV were orange crystalline substances, and XXI was a red crystalline substance; they were purified for analysis by crystallization from 80% acetic acid (IV), DMFA (V, VI, VIII, IX, XI-XIII, and XVIII-XIX), DMFA–methanol (1 : 1) (VII), glacial acetic acid (X, XIV), or DMFA–water (2 : 1) (XV, XVI, and XX).

3-(p-Dimethylaminophenyl)azomethino-7-methyl-2,3,5,8(1)-tetrahydroimidazo[1,2-*a*]pyrimidine-2,5-dione (XXII, Table 1). A 1.5-g (0.01 mole) sample of p-nitrosodimethylaniline and two to three drops of piperidine were added to a suspension of 1.65 g (0.01 mole) of I in 40 ml of absolute ethanol, and the mixture was refluxed for 15 h. The solvent was then evaporated, and the residue was washed with ether. The yield of XXII, which was obtained as brown crystals with mp 189-191° (dec., by reprecipitation from DMFA by the addition of water), was 1.2 g (40%).

3-Arylazo-7-methyl-2,3,5,8(1)-tetrahydroimidazo[1,2-*a*]pyrimidine-2,5-diones (XXIII-XXVI, Table 1). A) A mixture of 1.65 g (0.01 mole) of I, 1.7 g of anhydrous sodium acetate, and 0.011 mole of arenediazonium tetrafluoroborate in 15-20 ml of glacial acetic acid was heated on a boiling-water bath for 20-30 min, after which it was diluted with 50-60 ml of water, and the resulting precipitate was removed by filtration and washed successively with water and methanol to give XXIII-XXVI.

B) A 0.011-mole sample of the arenediazonium tetrafluoroborate was added to a solution of 1.65 g (0.01 mole) of I and 0.4 g (0.01 mole) of sodium hydroxide in 20-30 ml of water, and the mixture was allowed to stand at room temperature for 1.5-2 h. Water (50-60 ml) was added to it, and the resulting precipitate was removed by filtration and washed with water and methanol. The yields of XXIII, XXIV, and XXVI were 98, 99, and 69%, respectively.

Compounds XXIII and XXVI were yellow crystalline substances, while XXIV and XXV were orange crystalline substances; they were purified for analysis by crystallization from 80% acetic acid (XXIII), glacial acetic acid (XXIV and XXV), or DMFA – water (4 : 1) (XXVI).

LITERATURE CITED

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2. E. G. Knysh, A. N. Krasovskii, P. M. Kochergin, and P. M. Shabel'nik, Khim. Geterotsikl. Soedin., 399 (1972).