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SYNTHESIS AND PSYCHOTROPIC ACTIVITY OF 4-OXO-1-[HYDROXY(ACETOXY)PHENYL]-1,4-DIHYDROPYRIMIDINES

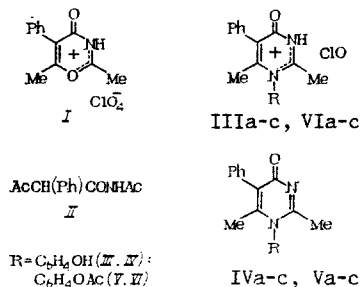
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The methods we have designed in our laboratory for converting salts of 4-oxo-1,3-oxazinium [10, 11] have opened up new possibilities for synthesizing the relatively little known 4-oxo-1,4-dihydropyrimidines [7, 8] which structurally resemble the heterocyclic fragment of the natural uridine nucleoside which exhibits a pronounced psychotropic (tranquiliizer and antidepressive) action [4, 5]. This also makes it imperative to undertake the synthesis of pyrimidines and to study their psychotropic activity for the purpose of making highly effective preparations.

A promising area of such study would seem to be the synthesis of 4-oxo-1,4-dihydropyrimidines and the simultaneous placement of biologically active fragments into their "nucleoside" position. One efficient way to accomplish that approach is the synthesis of 4-oxo-1,4-dihydropyrimidines with a hydroxyphenyl substituent (IV) and their modification by acylation, glycosylation and other reactions that involve a phenol hydroxyl.

In the present study we suggest methods for obtaining heretofore unknown pyrimidines IV by recycling 4-oxo-1,3-oxazinium perchlorate (I) [3] by replacing the cyclic oxygen with nitrogen (method A) or by heterocyclization of N-acetyl-2-phenylacetoacetamide (II) (method B) [13] and reaction with aminophenols. The syntheses are accomplished by boiling equimolar quantities of the starting substances in glacial AcOH [9] which acts both as the solvent and, apparently, a catalyst for the heterocyclization process in method B. The stable perchlorates of 4-oxopyrimidinium (III) that are initially formed in recycling by method A were quantitatively deprotonated into pyrimidones IV upon treatment with a NaHCO₃ solution.



The acetoxy derivatives Vb, c were obtained by reacting the corresponding pyrimidines with Ac₂O in the presence of catalytic quantities of HClO₄ as well as with AcCl in an

TABLE 1. 1-[Hydroxy-(acetoxy)-phenyl]-4-oxo-1,4-dihydroxy-pyrimidines and Their Perchlorates

Compound	Position of OH or OCOCH ₃ group	Yield, %	mp, °C	Empirical formula
IIIa	Ortho	95	167	C ₁₈ H ₁₇ N ₂ O ₆ Cl
IIIb	Meta	92	174	C ₁₈ H ₁₇ N ₂ O ₆ Cl
IIIc	Para	94	177	C ₁₈ H ₁₇ N ₂ O ₆ Cl
IVa	Ortho	94	312	C ₁₈ H ₁₆ N ₂ O ₂
IVb	Meta	99	299	C ₁₈ H ₁₆ N ₂ O ₂
IVc	Para	96	302	C ₁₈ H ₁₆ N ₂ O ₂
Va	Ortho	88	177	C ₂₀ H ₁₈ N ₂ O ₃
Vb	Meta	81	281	C ₂₀ H ₁₈ N ₂ O ₃
Vc	Para	89	266	C ₂₀ H ₁₈ N ₂ O ₃
VIa	Ortho	83	143	C ₂₀ H ₁₉ N ₂ O ₇ Cl
VIb	Meta	99	184	C ₂₀ H ₁₉ N ₂ O ₇ Cl
VIc	Para	96	257	C ₂₀ H ₁₉ N ₂ O ₇ Cl

Note. Compounds IVa, b, Vb, were recrystallized from ethanol; IVc, Va, c recrystallized from ethyl acetate; perchlorates IIIa-c and VIa-c from glacial AcOH.

alkaline medium. Acylation of pyrimidone IVa with a sterically screened o-phenol hydroxyl proceeds only in the presence of equimolar quantities of 70% HClO₄ with the formation of perchlorate VIa through whose deprotonation we also synthesized pyrimidone Va.

The synthesized pyrimidones IV, V, and their perchlorates III, VI are colorless crystals whose purity was confirmed chromatographically as well as by element analysis, and IR and PMR spectra. Data on the yields and properties of the synthesized compounds are given in Table 1.

The IR spectra of the 4-oxopyridinium perchlorates III and VI have a characteristic high-intensity absorption in the 1735-1700 cm⁻¹ region due to the C=O group stretch vibrations of the heterocyclic cation. The characteristic feature of this band is provided by the reversible shifting in the 1649-1628 cm⁻¹ region during the "deprotonation-protonation" processes. The fact that the C=O absorption band of salts III and VI are unaffected by the o-, m-, and p-substitutions of the OH group indicates the absence of a noticeable conjugation between the N-phenol and heterocyclic fragments of the molecule, and consequently, between their orthogonal position relative to each other. In the case of the pyrimidones IV and V, however, conjugation between these fragments may also exist. This is indicated by a certain lowering of the C=O absorption frequency during the transition from the o- and m- to the p-substituted isomer.

A second characteristic band for salts III and VI as well as for their acid analogs, the oxazinium salts I [3], is a medium strength band in the 1656-1648 cm⁻¹ band caused by the vibrations of the C(5)=C(6) bond which is amplified by a positive charge partially localized on the adjacent atom.

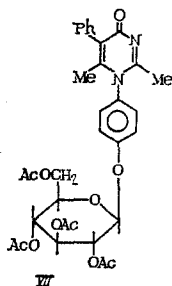
The spectra of the pyrimidones IV and V have a band in the 1543-1512 cm⁻¹ which disappears during protonation. We therefore attributed it to group C=N absorption. The OH group in the IR spectra is manifested in the form of diffuse absorption that is strongly displaced in comparison to the usual values in the 3000-2500 cm⁻¹ region. This is probably connected with a considerable intermolecular OH...O=C interaction with an ordered orientation of molecules in the crystalline state [1] since the resonance signals of the OH group in the NMR ¹H spectra of these solutions are manifested in the region in which the free phenols are usually found (~4 ppm).

The presence of phenol groups in the pyrimidones IV was confirmed also by a positive qualitative probe with ferric chloride and the appearance of broadened OH-absorption bands in the 3370-3280 cm⁻¹ region in the IR spectra of their perchlorates.

The formation of acetates was confirmed by the appearance of an acetoxyphenyl substituent absorption band in the IR spectra in the 1770-1762 cm⁻¹ region that only slightly shifts to the high-frequency region during protonation. The IR-spectra of the 4-oxopyridinium III and VI salts have a high-consistency band in the 1130-1045 cm⁻¹ region that is

characteristic for perchlorate-anion absorption, and a broadened weak NH-absorption band in the 3210-3180 cm^{-1} region.

The 2- and 6-methyl group signals of the pyrimidones in the NMR ^1H spectra are manifested in the 2.02-2.15 and 1.63-1.78 ppm regions, respectively. The weak polar shift experienced by the methyl group on the C(2) atom is due to its lowered electron density that results from the acceptor effect of the adjacent nitrogen atoms. When the electron-deficient C(2) atom is enlarged in the 4-oxopyridinium salts the signal of the 2-methyl group undergoes a further shift toward the weak field while the position of the 6-methyl group signal essentially remains unchanged.



The possibility of synthesizing O-glycosides from the phenol series of pyrimidones has been illustrated by the Koenigs-Knorr synthesis of O-glycoside VII by reacting aceto-bromoglucose with pyrimidone IVc.

EXPERIMENTAL CHEMICAL

IR spectra were recorded on a UR-20 spectrometer in a petroleum jelly suspension. NMR ^1H spectra were recorded on a Tesla BS-487C instrument (80 MHz) at 20°C in HMDS as the internal standard.

2,6-Dimethyl-5-phenyl-1-(4'-hydroxyphenyl)-4-oxopyridinium Perchlorate (IIIc). Method A. A 0.32 g (3 mmole) portion of p-aminophenol was added to 0.86 g (3 mmole) of 2,6-dimethyl-5-phenyl-4-oxo-1,3-oxazininium perchlorate (I) in 3 ml of glacial AcOH. The reaction mixture was boiled for 30 min, cooled, diluted with ether, filtered, and washed three times with ether. Yield was 1.10 g (94%) of IIIc.

The perchlorates of IIIa, b were obtained in a similar manner (see Table 1).

2,6-Dimethyl-5-phenyl-1-(4'-hydroxyphenyl)-4-oxo-1,4-dihydropyrimidine (IVc). Method B. A solution of 2.19 g (10 mmole) of N-acetyl-2-phenylacetoacetanilide (II) and 1.09 g (10 mmole) of p-aminophenol in 15 ml glacial acetic acid was heated for 1 h. The reaction mixture was cooled, diluted with water, and neutralized with Na_2CO_3 to pH 6.0. The precipitate was filtered, washed twice with water, and dried. Yield 2.8 g (96%). R_f 0.59 (Al_2O_3 , eluent 10:1 CHCl_3 -ethanol).

Pyrimidones IVa, b were obtained analogously (see Table 1).

2,6-Dimethyl-5-phenyl-1-(4'-acetoxyphenyl)-4-oxo-1,4-dihydropyrimidine (Vc). a). One drop of 70% HClO_4 was added to a suspension of 1.46 g (5 mmole) of pyrimidone IVc in 5 ml of Ac_2O , and the mixture was heated until it dissolved. The precipitate obtained upon heating on cooling on an ice bath was filtered and washed three times with ether. Yield was 1.49 g (89%). R_f 0.85 (Al_2O_3 , eluant CHCl_3 -ethanol, 10:1).

The pyrimidone Vb was obtained in a similar fashion.

b). A 0.34 ml (5 mmole) portion of AcCl was gradually added dropwise to a solution of 0.29 g (1 mmole) of pyrimidone IVc in 2.8 ml of 10% NaOH (1 mmole). The precipitate which formed 20 min later was filtered and washed with water until a neutral reading was obtained. Yield was 0.28 g (84%).

2,6-Dimethyl-5-phenyl-1-(2'-acetoxyphenyl)-4-oxopyridinium Perchlorate (VIa). A 1.5 ml (1.5 mmole) portion of 70% HClO_4 was added dropwise to a suspension of 0.43 g (1.5 mmole) of 4-oxo-1,4-dihydropyrimidine IVa in 1.5 ml of Ac_2O . After 30 min the mixture was cooled and diluted with ether. The precipitate was filtered off and washed twice with ether. Yield was 0.54 g (83%). The acetoxy-substituted perchlorates VIa, c were obtained by protonating the corresponding pyrimidines with 70% HClO_4 in glacial AcOH (see Table 1).

TABLE 2. Tranquilizing Activity of Pyrimidones (dose 12.5 mg/kg) in Rat Experiments

Compound	Number of approaches to the trough	Number of penalized drinks of water	Motor activity, number of upright stances
	M (boundaries of series)		
Control	10.9 (3-33)	2.8 (2-5)	4.75 (0-11)
IVa	18.8 (5-41)*	9.0 (3-34)**	11.40 (0-19)
IVb	3.4 (1-15)	4.25 (1-9)	2.13 (0-6)
IVc	19.5 (3-45)**	12.5 (5-44)***	7.60 (1-11)
Vb	11.6 (5-35)	5.25 (1-8)	2.14 (0-11)
Vc	20.1 (7-36)*	4.3 (1-8)	5.80 (2-12)

Note. One asterisk - $P_V < 0.05$; two asterisks - $P_V < 0.005$; three asterisks - $P_V < 0.001$ in comparison to the control.

TABLE 3. Antidepressive Activity of Pyrimidones in Mice Experiments

Compound	Dose, mg/kg	Duration of mice immobilization, sec M (boundaries of series)	Change in duration of immobilization, %
Control	—	68.5 (18-135)	100
IVa	12.5	81.0 (3-120)	118
	50.0	82.0 (25-200)	118
IVb	12.5	65.0 (30-105)	95
	50.0	81.0 (5-150)	131
IVc	12.5	50.6 (3-140)	74
	50.0	49.7 (25-90)	73
Vb	12.5	55.2 (15-95)	81
	50.0	36.0 (0-65)*	53
Vc	12.5	26.3 (0-55)**	38
	50.0	21.0 (0-60)*	31

Note. One asterisk - $P_V < 0.05$; two asterisks - $P_V < 0.01$; three asterisks - $P_V < 0.001$ in comparison to the control.

Deprotonation of the perchlorates IIIa-c and Va resulted in a quantitative yield by treating them with a saturated NaHCO_3 solution. In contrast to their acetates the pyrimidones IV turn a chloroform solution of FeCl_3 into a dark violet color upon the addition of pyridine.

Tetra-O-acetyl- β -(2,6-dimethyl-5-phenyl-4-oxo-1,4-dihydropyrimidine-1)-D-glucopyranoside (VII). An excess of acetobromoglucose is added in small portions to a solution of 2.92 g (10 mmole) of pyrimidine IVc in 10 ml of 10% NaOH until the mixture begins reacting vigorously. The reaction mixture is then heated on a water bath for 10 min, then cooled and the excess acetobromoglucose is filtered off. The filtrate is evaporated on a water bath and the residue is recrystallized from i-PrOH to yield 0.9 g (14%) of light yellow crystals, mp 172-173°C. R_f 0.27 (Al_2O_3 , eluant CHCl_3 , $[\alpha]_D^{18} +67$ (CHCl_3). IR spectrum, ν_{\max} , cm^{-1} : 1750 (OCOCH_3), 1630 (C=O), 1580, 1600, and 1520 (C=N and C=C_{arom}), 1255, 1235, and 1170 (C-O). NMR ^1H spectrum ($\text{CH}_3\text{OH-d}_4$). δ , ppm: 1.37 (3H, 6- CH_3), 2.28 (3H, 2- CH_3), 2.12-2.33 (12H, $\text{CH}_3\text{C=O}$), 2.72-3.95 (5H, H^{1-5}), 4.07 (2H, OCH_2), 6.95-7.75 (9H $_{\text{arom}}$).

EXPERIMENTAL PHARMACOLOGICAL

The tranquilizing and antidepressive properties of pyrimidones were examined by the "conflict situation" tests [6] and "tail suspension" test [12]. The neuroleptic properties were evaluated by the pyrimidines' effect on apomorphine-induced verticalization (AIV) of mice [14].

The experiments were performed on white non-linear male rats (weighing 150-250 g) and mice of both sexes (weighing 18-25 g).

The substances were administered orally to the animals 60 min before testing at doses of 12.5-50.0 mg/kg.

The experimental results were statistically processed employing the nonparametric Wilcoxon-Mann-Whitney V criterion [2].

Our examination of the tranquilizing properties of pyrimidines demonstrated that pyrimidone IVc exhibits the most pronounced effect. A somewhat lesser effect, as measured by the number of penalized drinks of water, was exhibited by pyrimidone IVa. Pyrimidone IVb merely exhibited a tendency to manifest those properties (Table 2).

Tranquilizing activity was also exhibited by pyrimidone Vc which increased the number of rat approaches to the feeding trough. A statistically reliable antidepressive action was exhibited by the pyrimidones V which at a dose of 50 mg/kg reduced the duration of immobilization which constitutes a behavioral manifestation of a depressive-like state (DLS) of animals [12]. The most pronounced effect was induced by pyrimidone Vc.

In contrast to V, the pyrimidones IV do not exhibit a clear effect on the total duration of immobilization (Table 3) and exhibit a variably directed action. Thus, whereas pyrimidone IVc was found to have a tendency to reduce the DLS at doses of 12.5 and 50 mg/

TABLE 4. Neuroleptic Activity of Pyrimidones in Mice Experiments

Compound	Dose, mg/kg	Scored degree of AIV after administration of Apo (in min)		Number of mice with maximum degree of AIV, %
		5 min	10 min	
Apo (control)				
IVa + Apo	2.0	2.4	3.4	62
IVb + Apo	50.0 ± 2.0	2.4	3.9	85
IVc + Apo	50.0 ± 2.0	2.9	3.6	100
IVd + Apo	50.0 ± 2.0	1.9	3.0	53
Vb + Apo	25.0 ± 2.0	3.0	3.9	100
Vb + Apo	50.0 ± 2.0	1.8	2.8	43
Vb + Apo	75.0 ± 2.0	2.3	3.7	86
Vc + Apo	50.0 ± 2.0	1.0*	2.0*	50

* $P_V < 0.05$ in comparison to the control.

kg, pyrimidone IVa, and particularly IVb, exhibited a tendency to increase that duration by 31%.

A comparative evaluation of the effect that pyrimidones have on AIV in mice showed that pyrimidone Vc, while reliably reducing AIV at a dose of 50 mg/kg (Table 4), reduces the number of mice in which the AIV is maximum. At a dose of 50 mg/kg pyrimidone Vb also reduces the number of mice with pronounced AIV and exhibits a strong tendency to reducing AIV. At a dose of 25 mg/kg this compound induces the opposite effect, i.e., the AIV in mice is increased.

The pyrimidones IV are shown not only to exhibit neuroleptic properties, but on the contrary, as illustrated by IVb, increased AIV in mice at a dose of 50 mg/kg (see Table 4).

The effect of attenuating the effect of apomorphine (Apo) by pyrimidones is evidently analogous to the mechanism underlying the action of typical neuroleptics [14] and is attributed to their ability to block the postsynaptic dopamine receptors (D_2) of the cerebral mesolimbic structures, while at the same time attenuating the action of Apo, a direct agonist of the D_2 -receptors. In that connection, the effect of the pyrimidones which intensify AIV in mice is probably associated with their modulating influence on the D_2 -receptors.

An analysis of our experimental results indicates that the pyrimidones possess a tranquilizing, antidepressive, and neuroleptic type of psychotropic action.

The nature and position of the substituent in the N-aryl ring has a significant influence on the nature and intensity of pyrimidones psychotropic activity.

One can see from Tables 2-4 that the pyrimidones of the IV phenol series exhibit tranquilizing activity whereas their acetates possess antidepressive and neuroleptic activity which is significantly greater in the pyrimidones containing an OH- or $OCOCH_3$ group in the p-position of the N-aryl ring. The introduction of substituents in the m-position of the N-aryl ring (see Table 4) accords the pyrimidones, in contrast to their para-substituted analogs, the ability to amplify the effect of Apo on the D_2 -receptors.

Thus, our study of the interconnection between chemical structure and psychotropic action opens up new prospects for finding highly effective pharmacological preparations that combine tranquilizing, anti-depressive, and neuroleptic properties among the 4-oxo-1, 4-dihydropyrimidine series that contain substituents in the p-position of the N_1 -phenyl ring.

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SYNTHESIS AND ANALGESIC ACTIVITY OF 4-ANILIDES OF 1-SUBSTITUTED-2,5-DIMETHYLPYPERIDINES

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The 4-anilinopiperidines are currently the strongest class of analgesics used in medical practice. The atoms and groups responsible for the analgesic activity are those capable of donor-acceptor interactions with an appropriate receptor system. However, it is well known that activity of these compounds can be significantly affected when groups and atoms are introduced that are not capable of such interactions. For example, the analgesic action of the 4-phenylpiperidine series is significantly elevated when methyl substituents are introduced into the piperidine ring.

The availability of 1-alkyl-2,5-dimethyl-4-piperidones [2] has made it possible to synthesize a series of the 4-anilinopiperidine class of compounds that are analogs of the widely used narcotic analgesic fentanyl [4, 6, 7] that possess the presumed analgesic activity, and has allowed us to draw some specific conclusions about the structure-action relationship.

The pattern employed for the synthesis of the compounds under examination includes the condensation of the corresponding ketones I with aniline, followed by the reduction of the Schiff bases to phenylamines III and subsequent acylation by anhydrides or chloroanhydrides of the acids to compound IV. The type of substitution on the nitrogen atom of the piperidine ring and the acyl fragment on the aniline nitrogen atom was varied. In order to clarify the role of the carbonyl group in the amide portion of the molecule the latter was reduced to the corresponding amine V. By condensing the starting ketones with benzylamine and by repeating the aforementioned operations, we obtained the benzylamines in which the aromatic ring of the aniline fragment was removed to one methylene group. Finally, we undertook the synthesis of compound VIII in which the amide nitrogen atom was replaced by a carbon atom. The latter was synthesized by condensing the starting piperidines I with benzylcyanide followed by the selective reduction of the conjugated double bond of compound VI to the nitrile VII. Ethyl magnesium bromide was then reacted with the resultant nitriles in a Grignard reaction (see scheme on following page).

Biological tests of the compounds under study showed that the series of these derivatives as a whole characteristically exhibit morphine-like analgesic action.

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