SYNTHESIS AND FUNGICIDAL ACTIVITY OF SUBSTITUTED 4-AMINOPIPERIDINES AND 4-AMINOTETRAHYDROPYRIDINES

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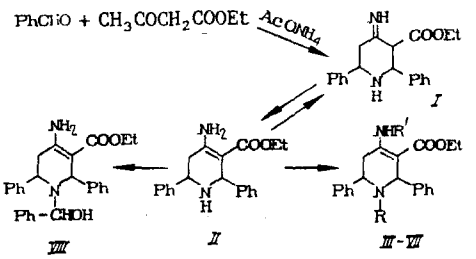
In continued work [2] on the synthesis and study of the pesticidal activity of derivatives of piperidine we turned to the preparation of new substituted piperidine and tetrahydropyridines containing an amino- or an amido-group in position C(4). Condensation of benzaldehyde with acetoacetic ester in the presence of $AcONH_4$ after treating the reaction mixture with hydrochloric acid gave 2,6-diphenyl-3-carboethoxy-4-iminopiperidine (I), in the form of the hydrochloride. Action of aqueous ammonia on the hydrochloride gave the enamine form of the imine, i.e., the substituted 4-amino-1,2,5,6-tetrahydropyridine (II), which could be transformed into compound I by dry HCl in absolute ether. This established the 4-imino – 4-enamine transformation in the 2,6-diphenyl-3-carboethoxypiperidine series.



R=Ac (III, IV), COEt (V), CONHPh (VI), CSNHPh (VII);
R'=H (III, VI, VII) Ac (IV), COEt (V).

Prolonged heating of amine II with Ac_2O leads to acetylation only of the cyclic primary amino groups and the formation of the monoacetyl derivative III, obtained in quantitative yield. Lengthy heating of compound II with Ac_2O or with $(EtCO)_2O$ leads to the diacyl derivatives IV and V in yields of over 55%. Condensation of compound II with phenyl isocyanate or with phenyl isothiocyanate takes place at the primary amino group to form the 1-phenylcarbamoyl(thiocarbamoyl) derivative of the 4-aminotetrahydropyridines VI and VII. Condensation of compound II with benzaldehyde in the presence of AcOH gives 1-(o-hydroxybenzyl)-4-aminotetrahydropyridine (VIII) instead of the azomethine, the product of condensation on the primary amino group, in a yield of 45%. Under acidic conditions the enamine II is hydrolyzed to 2,6-diphenyl-3-carboethoxypiperidine-4-one [5].

In [4] it was shown that acylation of NH-piperidine-4-one with an aryl substituent in the ring gives the ester of the enol forms. In this connection there was interest in a study of the acylation of the oximes of γ-piperidone, which may exist as the N-oximino and the N-hydroxyenamine forms. Upon treatment of the oxime of 2,3,6-triphenylpiperidin-4-one (IX) with Ac_2O in pyridine, 1-acetyl-2,3,6-triphenyl-4-(N-acetoxyimino)piperidine (X) was formed in 60% yield. Treatment under analogous conditions of the same oxime of IX with $(EtCO)_2O$ gave derivatives of its N-hydroxyenamine forms; 1-propionyl-4-(N-hydroxy-N-propionylamino)- and 1-propionyl-4-(N-propionyloxyamino)-2,3,6-triphenyl-1,2,5,6-tetrahydropyridines(XI, XII) in a ratio of 1:0.6.

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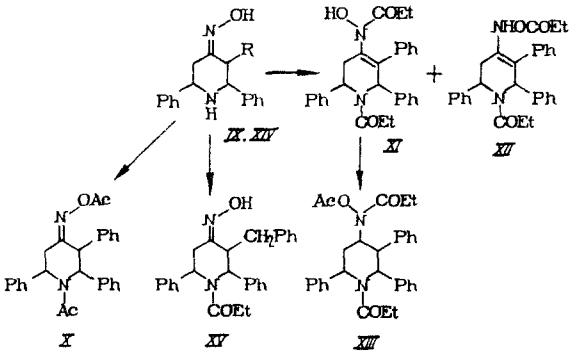
TABLE 1. Characteristics of the Synthesized Compounds

Compound	Yield, %	MP, °C	IR Spectrum, ν_{max}, cm^{-1}	Empirical formula	M^+ (Mass Spectrum)
I	80	211—4	3420 b, 3156 b 1753, 1720, 1650	$C_{20}H_{22}N_2O_2$	322
I·HCl	28	203—5	3420 b, 2800—2380 b, 1690	$C_{20}H_{22}N_2O_2 \cdot HCl$	—
II	27	150—2	3500, 3350, 1682, 1620	$C_{20}H_{22}N_2O_2$	322
III	80	206—8	3432, 3320, 3240, 1682, 1632	$C_{22}H_{24}N_2O_3$	364
IV	58	132—5	—	$C_{24}H_{26}N_2O_4$	406
V	55	181—4	3256, 3216, 1730, 1650 sh 1642, 1632	$C_{26}H_{30}N_2O_4$	436
VI	58	195—6	3422, 3316, 3236, 1676, 1650, 1636	$C_{27}H_{27}N_3O_3$	441
VII	63	150—2	3475, 3371, 3352, 1680, 1643	$C_{27}H_{27}N_3O_2S$	457
VIII	45	155	3420, 3308, 3296, 3226, 3184, 1680, 1625	$C_{27}H_{28}N_2O_3$	428
X	62	188—9	1782, 1652	$C_{27}H_{26}N_2O_3$	426
XI	25	210	3271, 1674 sh 1662, 1632	$C_{29}H_{30}N_2O_3$	454
XII	10	234—5	3302, 1747, 1690, 1678 sh 1631	$C_{29}H_{30}N_2O_3$	454
XIII	80	185	1728, 1712 sh 1676	$C_{31}H_{32}N_2O_4$	496
XV	76	170	1652 sh 1642 sh 1612 wide	$C_{27}H_{28}N_2O_2$	412
XVIII	14	—	1666, 1635 sh	$C_{16}H_{22}N_2O$	258
XIX	22	—	1650 wide	$C_{17}H_{24}N_2O$	272
XX	51	—	1650	$C_{21}H_{24}N_2O$	320
XXI	24	—	1650	$C_{17}H_{20}N_2O$	272
XXII	54	—	1645	$C_{18}H_{22}N_2O$	286
XXIII	40	—	1650 wide 1620 sh	$C_{22}H_{26}N_2O$	334
XXIV	30	173—4	1740	$C_{31}H_{19}NO$	431
XXV	70	143—4	3379	$C_{31}H_{32}N_2$	432
XXVI	85	150—1	1632	$C_{38}H_{36}N_2$	520
XXVII	72	134—5	3450 b	$C_{38}H_{38}N_2$	522
XXVIII	47	92—3	1660	$C_{41}H_{42}N_2O$	578
XXIX	65	210—2	1652	$C_{31}H_{30}N_2$	430
XXX	17	75—7	1790, 1747, 1679	$C_{43}H_{42}N_2O_8$	714

The action of Ac_2O on compound XI gave the product of acetylation upon the N-hydroxygroup: 1-propionyl-2,3,6-triphenyl-4-(N-propionyl-N-acetyloxyamino)-1,2,5,6-tetrahydropyridine(XIII). Treatment with $(EtCO)_2O$ of the oxime of 2,6-diphenyl-3-benzylpiperidin-4-one (XIV) containing an electron donor group in the β-position produces acylation only on the piperidine nitrogen atom. In this case the oxime of 1-propionyl-2,6-diphenyl-3-benzylpiperidin-4-one (XV) was formed in quantitative yield. Thus, the direction of acylation of oximes of γ-piperidones substituted with aryl groups in the ring depends both on the nature of the acylating agent and on the nature of the substituent in position C(3).



R=Ph (IX), CH_2Ph (XIV)

Characteristic absorption bands for the amide groups are observed in the IR spectra of compounds XI and XII (cf. Table 1). The ester CO-groups of piperidine XII absorb at 1743 cm^{-1} and its NH-group at 3302 cm^{-1}. The associated OH-group of the diamide XI is in the form of a wide band at 3271 cm^{-1}, which is absent in the IR spectrum of the acylated product XIII. The position of the double bond at C(3)—C(4) in compounds XI-XIII unequivocally follows from ^1H NMR spectral data (cf. Table 2) and is determined by the opportunity of conjugation with the phenyl radical in position C(3).

N,N-disubstituted 4-amino-1,2,5,6-tetrahydropyridines XVIII-XXIII form in moderate yield upon reaction of 1,2,5-trimethyl-4-N-phenyl(benzyl)iminopiperidines (XVI, XVII) [1, 3] with acyl chlorides in the presence of Et_3N.

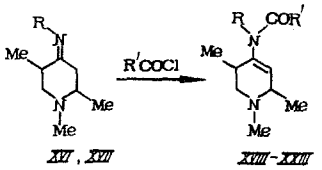
TABLE 2. ^{1}H NMR Spectra of the Synthesized Compounds (in $CDCl_3$)

Compound	Chemical Shift, δ, ppm (Multiplicity, KSSK, J, Hz)									
	Piperidine Ring Protons						CH_3	CH_2	Aromatic Protons	Other protons
	1	2	3	4	5a, 5f	6				
I·HCl	11.4 (br.s)	In arom. Reg.	5.26 (br.s)		3.36 (dd, 18.2 and 10.8), 2.85 (dd, 18.2 and 5.	4.24 (brs.)	0.96 (t)	4.08 (q)	7.24–7.80 (m)	10.05 (br.s C(4)=NH), 12.48 (s HCl
I+	3.43 (br.s)	5.09 (br. s)	6.80 (br.s)		3.76 (m) 2.84 (m)	5.24 (br.s)	0.96 (t)	3.96 (q)	7.30–8.00 (m)	8.08 (s, C (4)=NH)
II	1.96 (br.s)	4.90 (t)	–	–	2.20 -2.80 m)	4.00 (b)	0.75 (t)	3.73 (q)	7.10–7.40 (m)	6.10 (br.s, NH_2)
IV	–	In arom. R	–	–	4.33 (m)	5.00 (br.s 10) (t) (s)	2.2 (t) 2.0 (s)	4.00 (q)	7.00–7.43 (m)	11.43 br.s NHCO)
V	–	7.00	–	–	4.43 (m), 3.18 (dd 9.0 d 2.5)	5.50 (br.s)	1.33 (t) 1.5 (b.	4.43 (q),	7.18–7.50 (m)	11.28 (br.sNHCO)
VI	–	6.33 (s)	–	–	2.67 (q) 15 and 12), 2.2 (q, 15 and 5)	4.77 (q, 12 and 5)	1.1 (t) 1.2 (t)	2.25 (q 2CH_2) 4.18 (q.)	6.90–7.75 (m)	NH_2, CONH in arom. reg.
VII	–	In arom. Reg.	–	–	2.75 (q) 15 and 12), 2.3 (q. 15 and 5)	4.96 (q, 12 and 5)	1.22 (t)	4.2 (q)	6.95–7.75 (m)	8.4 (s, CSNH)
VIII	–	5.20 (s)	–	–	2.63 (q) 16.5 and 10), 2.43 (q, 16.5 and 4.8)	4.03 (m)	0.90 (t)	3.95 (q)	7.15–7.62 (m), 8.00–8.17 (m, 2H 8 and 2)	6.1 br.s NH_2 · OH)
X	–	6.25 (br.s)	5.10 (d., 1.8)	–	3.00 (m)	5.10 (t. 4.2)	1.67 (s), 1.92 (s),	–	7.0–7.50 (m)	–
XI	–	6.97 (d, 4.0)	–	–	2.00 (m)	6.97 ((br.s)	0.95 (t), 1.20 (t),	2.35 (q) 2.00 (q)	7.25–7.65 (m)	–
XII	–	6.45 (br.s)	–	–	1.95 (m). 2.50 (m)	5.60 (br.s)	1.20 (t), 1.30 (t)	2.35 (q) 2.65 (q)	6.70–7.50 (m)	1.70 (br.sNH)
XV	–	5.76 (d. 2.6)	2.85 (m)	–	3.50 (m). 2.80 (m)	5.58 (t 3.3)	1.05 (t)	2.35 (q) 2.93 (d)	7.00–7.30 (m)	10.7 (s, N=CH)
XVIII	–	2.5 -2.85 (m)	4.41 (br.s)		2.41 (m)	3.1 (q), 2.5–2.85 (m)	0.95 (d), 1.13 (d)	–	6.65–7.36 (m)	2.33 (s $COCH_3$) 2.36 (s NCH_3)
XIX	–	2.5 –2.8 (m	5.78 (br.s)	–	2.35 (m)	3.15 (q, 6.0), 2.5–2.8 (m)	0.95 (d), 1.13 (d), 1.18 (d)	2.35 (m)	6.59–7.65 (m)	2.38 (s NCH_3)
XX	–	2.7 (m)	5.13 (d. 2.6)	–	3.50 (m)	2.60 (m)	0.88 (d), 1.30 (d)	–	7.00–7.70 (m)	2.30 (s NCH_3)
XXI	–	2.63 (m)	5.16 (d. 2.6)	–	2.41 (m)	2.44 (m). 2.54 (m)	1.03 (d), 1.05 (d)	4.40 (d) 4.72 (d)	7.23–7.30 (m)	2.24 (s NCH_3), 2.03 (s $COCH_3$)
XXII	–	2.30 (m)	5.03 (d 2.6	–	2.62 (m)	2.54 (m 2H)	1.10 (d), 1.13 (d), 1.18 (d)	4.40 (d), 4.85 (d)	7.18–7.36 (m)	2.30 (s NCH_3), 2.41 (q. $COCH_2$)
XXIII	–	2.21 (m)	4.82 (br.s)	–	2.25 (m)	2.40 (m. 2H)	0.70 (d), 0.75 (d)	4.79 (d) 4.97 (d)	7.04–7.65 (m)	2.13 (s. NCH_3)
XXIV	–	3.65 –3.85 (m)	–	2.40 (. 10.5)	2.75 (m) 2.90 m,	3.65 –3.85 (m)	–	2.40 (m)	–	–
XXV	–	3.70 (d 10)	2.80 (m	3.10 (m)	1.6–2.2 (m)	3.90 (m)	–	2.00 (m)	–	2.00 (br.s NH_2)
XXVI	–	3.95 (d 10)	3.35 (t 10)	3.80 (m)	2.45 (m), 2.05 (m)	4.00 (m,	–	2.45 (s 4H)	6.40–7.70 (m)	7.85 (s, N=CH)
XXVII	–	3.66 (d 8)	3.00 (m	3.80 (m)	2.35 m), 2.00 (m)	3.86 (m)	–	2.45 (s) 4H) 1.75 (t	6.40–7.60 (m)	1.80 (br.s NH)
XXVIII	–	3.95 (d)	3.10 (m)	4.60 (m)	1.8–2.2 (m)	4.20 (m)	1.20 (t)	3.45 (q), 2.45 (s, 4.36 (br.s	6.35–7.70 (m)	–
XXIX	–	3.5–3.9 (m)	3.35 (t 10)	3.5–3.9 (m)	2.4 (m), 2.05 (m)	3.5–3.9 (m)	1.80 (s)	–	6.85–7.65 (m)	7.85 (s, N=CH)
XXX	–	3.1–3.5 (m)	1.65–2.1 (m)	3.1–3.5 (m)	1.65–2.1 (m)	3.1–3.5 (m)	3.5–4.0 (4CH_3)	–	6.80–7.60 (m)	1.25 (s, NCH_3), 3.1–3.5 (m 2H)

Notes. +) in DMSO; ++) 2- and 3-protons give doublet signals at 4.2 and 4.73 ppm with J = 10.4 Hz upon plotting the spectrum in D_6-pyridine.

TABLE 3. Fungicidal Activity of the Synthesized Compounds (indicating percent depression of the development of bacteria. The micelles of fungus or mold compared with the control)

Activity of the Compounds (Test Objects)	Compounds										
	I	II	II·CH_3I	IV	VI	VIII	X	XX	XXI	XXII	XXIII
Bactericidal (Xanthomonas malvacerum)	0	50	36	50	44	0	43	21	33	36	17
(Fusarium gram.)	0	4	10	24	0	0	34	2	0	2	0
(Rhizoctonia solanis)	0	50	32	70	10	50	40	34	62	24	42
Tomato Phytophthora	0	0	0	0	0	3	0	—	18	75	14
Bean Botrytis Rod	12	0	75	0	0	0	0	—	44	0	18

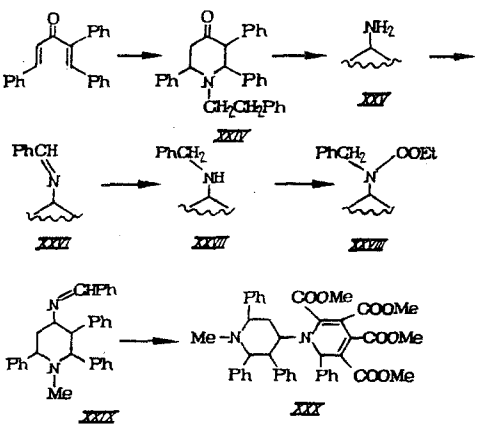


R=Ph (XVI, XVIII—XX), CH_2Ph (XVII, XXI—XXIII);
R'=Me (XVIII, XXI), Et (XIX, XXII), Ph (XX, XXIII)

In the ^1H NMR spectral data of compounds XVIII-XXIII (cf. Table 2) the presence of two doublet signals for the protons of the CH_3-groups at C(2) and C(5), and also the presence of weak signals (at 4.4-5.8 ppm) in the form of broad singlets or doublets for the vinyl protons at C(3) show that the double bonds in the chromatographically isolated amides are found on C(3)—C(4) of the rings. Their constraint into this position is presumably promoted by the potential for compressing the fragment C(3)—C(4)—N—C—O by means of π-conjugation. A similar coplanarity would result in steric hindrance in the case of the more advantageous substitution of the double bond in position C(4)—C(5).

With the aim of studying the physiological activity of structural analogs of the analgetic fentanyl with three phenyl substituents in the piperidine ring, we successively synthesized 4-oxo(XXIV)-, 4- amino(XXV)-, 4-benzylidenylamino(XXVI)-, 4-benzylamino(XXVII)-, and 4-N-benzyl-N-propionylamino(XXVIII)-1-(β-phenylethyl)-2,3,6-triphenylpiperidines, starting from 1,2,5-triphenyl-1,4-pentadien-4-one.

In order to obtain derivatives of piperidine with a tertiary amino group in the 4-position a condensation was carried out between 1-methyl,2,3-6-triphenyl-4-benzylidenylaminopiperidine (XXIX) with the dimethyl ester of acetylene dicarboxylic acid. With a ratio of starting materials of 1:2, the cyclic 1:2 adduct was formed in a yield of 17%.



According to IR and ^1H NMR spectral data the structure of the cyclocondensation product corresponded to 1-methyl-2,3,6-triphenyl-4-(2'-phenyl-3',4',5',6'-tetramethoxycarbonyl-1',2'-dihydropyridine-1'-yl)piperidine (XXX),

Characteristics of the synthesized compounds and their ^1H NMR spectra are presented in Tables 1 and 2.

A study of the pesticidal activity of 11 of the synthesized compounds was carried out according to the method of [2]. With respect to herbicidal activity, all materials proved to be inactive upon pre-emergent application, and upon application to the vegetation they possessed weakly significant activity. Imine I did not show toxic action against the studied bacteria, fungus micelles, and diseases of green plants (cf. Table 3). Its tautomeric form, the enamine II, possessed a range of bactericidal and fungicidal (against Rhizoctonia solanis) activity. It was inactive in experiments in vivo in the form of the free base, but its iodomethylate showed significant fungicidal activity against bean botrytis rot (75%). Introduction of hydroxybenzyl groups into position N(1) of enamine II eliminates bactericidal activity with preservation of the moderate toxicity to R. solanis fungus micelles. In addition, the moderate bactericidal activity and the increase in fungicidal activity of the diamide IV against R. solanis (70%), correlate with the activities of the starting enamine II. The 1,2,5-trimethylsubstituted piperidines (XX-XXIII), acylated on the amino groups, possess little significant bactericidal activity and moderate fungicidal activity against R. solanis. An appreciable increase in the toxicity of these materials was observed upon substitution of the propionyl group on the amide fragment (24%) by the benzoyl (42%) and particularly by the acetyl group (62%). It should be noted that there is significant fungicidal activity in the amide XXII against tomato phytophthorosis (75%).

Amine XXV possesses low toxicity ($LD_{50} > 1000$ mg/kg). In tests of its psychotropic activity, a weakly stimulatory effect was discovered with a weak inhibitory activity on the action of acetylcholinesterase. In addition, it showed moderately significant antistaphylococcal effect. Because of its high acute toxicity, the analgetic properties of compound XXVIII hydrochloride could not be shown.

EXPERIMENTAL

The ^1H NMR spectra were recorded on a Bruker WP-80 (80 MHz) instrument in $CDCl_3$. IR spectra were obtained on an IR-20 spectrometer (in KBr pellets) or on a Specord IR-75 (as films). Mass-spectra were obtained with a MX-1303 spectrometer. The values found for elemental analyses corresponded with the calculated values.

2,6-Diphenyl-3-carboethoxy-4-iminopiperidine (I). A mixture of 52 g (0.4 mole) of acetoacetic ester, 84.4 g (0.8 mole) of benzaldehyde and 30.8 g (0.79 mole) of $AcONH_4$ in 20 ml of glacial acetic acid was heated to boiling, then cooled and mixed with 400 ml of ether, 40 ml of water, and 40 ml of conc. HCl. The resulting precipitate was separated, washed with ether, dried, and recrystallized from alcohol to give 40 g of the hydrochloride of I.

2,6-diphenyl-3-carboethoxy-4-amino-1,2,5,6-tetrahydropyridine (II). To a solution of 40 g (0.11 mole) of the hydrochloride of I in 100 ml of aqueous alcohol at 0°C was added 50 ml of 25% solution of aqueous ammonia. The resulting precipitate was freed from solvent and dried to give 9.6 g of compound II as colorless crystals after recrystallization from acetone. Mass-spectrum, m/z (%): 322 (23), 293 (20), 275 (9), 249 (19), 245 (100). The iodomethylate of II crystallized in yellow crystals, mp = 173-175°C.

Upon passing dried HCl gas through a solution of 1.0 g (3.1 mmoles) of enamine II in 10 ml of absolute alcohol, 0.8 g of compound I was obtained as colorless crystals. Mass-spectrum, m/z (%): 322 (93), 255 (52), 250 (54), 246 (100).

Upon hydrolysis of the enamine II (conc. H_2SO_4, 20°C, 12 h), 2,6-diphenyl-3-carboethoxypiperidin-4-one was obtained in 50% yield.

1-Acetyl-2,6-diphenyl-3-carboethoxy-4-amino-1,2,5,6-tetrahydropyridine (III). A solution of 1.3 g (4.0 mmoles) of compound II in 5 ml of Ac_2O was heated to boiling and kept for 18 h at 20°C. The reaction mixture was added to ice and the precipitate was collected, washed with water, and dried to give 1.2 g of compound III, yellow crystals. Mass-spectrum, m/z (%); 364 (100), 318 (6), 306 (33).

1-Acetyl-4-acetylamino-2,6-diphenyl-3-carboethoxy-1,2,5,6-tetrahydropyridine (IV). Analogously, after boiling 1.2 g (3.7 mmoles) of compound II for 10 h in a mixture of 4 ml of Ac_2O and 2 ml of pyridine to give 0.7 g of compound IV, yellow crystals after recrystallization from acetone.

1-Propionyl-4-propionylamino-2,6-diphenyl-3-carboethoxy-1,2,5,6-tetrahydropyridine (V). Analogously from 2.0 g (6.2 mmoles) of compound II, 6.5 ml of $(EtCO)_2O$ and 4 ml of pyrimidine to give 1.5 g of compound V in the form of yellow crystals.

4-Amino-3-carboethoxy-2,6-diphenyl-1-phenylcarbamoyl (VI)- and -1-phenylthiocarbamoyl (VII)-1,2,5,6-tetrahydropyridines. A mixture of 1.0 g (3.1 mmoles) of enamine II and 1.5 ml (12 mmoles) of phenylisocyanate in 25 ml of absolute benzene was stirred at 20°C for 4 h. The benzene was distilled and the residue was crystallized from $CHCl_3$ to give 0.8 g of compound VI. Analogously, 1.0 g (3.1 mmoles) of compound II and 1.7 ml (12 mmoles) of phenylisocyanate gave 0.9 g of compound VII.

4-Amino-3-carboethoxy-1-(α-hydroxybenzyl)-2,6-diphenyl-1,2,5,6-tetrahydropyridine (VIII). A mixture of 2.0 g (6.2 mmoles) of compound II and 0.66 ml of benzaldehyde in 40 ml of absolute benzene was boiled for 5 h in the presence of a catalytic amount of AcOH. After distillation of the benzene the residue was crystallized from acetone to give 1.2 g of compound VIII in the form of pale crimson crystals.

1-Acetyl-2,3,6-triphenyl-4-acetoxyiminopiperidine (X). A mixture of 10.0 g (0.029 mole) of oxime IX, 61.0 g (0.3 mole) of Ac_2O and 5 ml of pyridine was heated at 70°C and then kept for 12 h at 20°C. Soda solution was added to pH 8, and the reaction mixture was extracted with ether and the extract was dried with $MgSO_4$. Removal of the ether gave 4.7 g of compound X.

1-Propionyl-2,3,6-triphenyl-4-(N-hydroxy-N-propionylamino)- and 4-(N-propionyloxyamino)-1,2,5,6-tetrahydropyridines (XI and XII). Analogously, 10.0 g (0.029 mole) of oxime IX, 103 ml (0.82 mole) of $(EtCO)_2O$ and 5 ml of pyridine gave 2.3 g of compound XI in the form of yellow crystals. The residue from the mother liquor was chromatographed on silica gel (eluent = 3:1 ether/pentane). Early eluents gave 1.0 g of compound XI and then 1.33 g of compound XII in the form of colorless crystals.

1-Propionyl-2,3,6-triphenyl-4-(N-propionyl-N-acetyloxyamino)-1,2,5,6-tetrahydropyridine (XIII). A mixture of 1.6 g (3.5 mmoles) of compound XI, 40 ml (0.42 mole) of Ac_2O and 2 ml of pyridine was boiled for 5 h. The reaction mixture was cooled by the addition of ice and the product was extracted with ether. The residue after removal of the solvent was recrystallized from acetone to give 1.4 g of compound XIII in the form of colorless crystals.

1-Propionyl-2,6-diphenyl-3-benzyl-4-hydroxyiminopiperidine (XV). Analogously to the synthesis of compound X, from 10.0 g (0.28 mole) of oxime XIV, 100 ml (0.8 mole) of $(EtCO)_2O$ and 5 ml of pyridine to give 9.0 g of compound XV.

1,2,5-Trimethyl-4-[N-phenyl(benzyl)-N-acetyl(propionyl, benzoyl)amino]-1,2,5,6-tetrahydropyridines (XVIII-XXIII). To a solution of 0.01 mole of imine XVI (XVII) and 0.01 mole of Et_3N in 50 ml of absolute ether cooled to 5°C was added dropwise a solution of 0.01 mole of acid chloride in 50 ml of ether. The mixture was stirred at this temperature for 3 h and was kept for 12 h at 20-25°C. The precipitate of $Et_3N \cdot HCl$ was separated and the solution was washed successively with water, salt solution, water, and dried with $MgSO_4$. The residue after distillation of the ether was chromatographed on alumina (eluent = 1:10-1:20 ethyl acetate/pentane) to give amides XVIII-XXIII as light yellow oils.

1-(β-Phenethyl)-2,3,6-triphenylpiperidin-4-one (XXIV) was prepared according to the method of [2] from 0.1 mole of 1,2,5-triphenyl-1,4-pentadien-4-one and 0.1 mole of β-phenethylamine.

1-(β-Phenethyl)-2,3,6-triphenyl-4-aminopiperidine (XXV). To a boiling solution of 5.2 g (0.012 mole) of piperidone XXIV oxime (prepared from ketone XXIV, mp 198-199°C) in 35 ml of absolute ethanol was added portionwise 26.0 g (1.13 moles) of sodium. The mixture was boiled for 3 h, 15 ml of alcohol was distilled, and to the residue was added 150 ml of water. The mixture was extracted with ether and the extract was dried with Na_2SO_4. Removal of the ether and crystallization of the residue from ethanol gave 4.9 g of amine XXV as colorless crystals.

1-(β-Phenethyl)-2,3,6-triphenyl-4-benzylidineaminopiperidine (XXVI). A solution of 2.5 g (5.78 mmoles) of amine XXV, 1 ml (8.7 mmoles) of benzaldehyde and 1 ml of glacial AcOH was boiled for 8 h in 60 ml of dry toluene until no more water was removed. The toluene was distilled, and the residue was recrystallized from ether. The resulting crystals were recrystallized from ethanol to give 2.55 g of compound XXVI.

1-(β-Phenethyl)-2,3,6-triphenyl-4-benzylaminopiperidine (XXVII). To a solution of 4.5 g (8.6 mmoles) of imine XXVI in 60 ml of ethanol was added in portions with stirring 3.27 g (86 mmoles) of $NaBH_4$. The reaction mixture was stirred for 3 h, then poured into water. The resulting precipitate was filtered off and recrystallized from a mixture of ethanol and hexane (1:1) to give 3.21 g of compound XXVII.

1-(β-Phenethyl)-2,3,6-triphenyl-4-(N-benzyl-N-propionylamino)piperidine (XXVIII). A mixture of 1.0 g (1.9 mmoles) of benzylaminopiperidine XXVII and 2.5 g (19 mmoles) of $(EtCO)_2O$ in 5 ml of pyridine was heated for 1 h. The pyridine and excess anhydride were distilled and the residue was treated with 20% salt solution, extracted with ether, and dried with $MgSO_4$. Removal of the ether gave 0.51 g of compound XXVIII as yellow crystals. Mass spectrum m/z (%): 578 (1), 487 (57), 325 (45), 91 (100).

1-Methyl-4-(2'-phenyl-3',4',5',6'-tetramethoxycarbonyl-1',2'-dihydropyridin-1'-yl)-2,3,6-triphenylpiperidine (XXX). A solution of 0.75 g (1.7 mmoles) of imine XXIX, prepared from 1-methyl-2,3,6-triphenylpiperidin-4-one analogously to the synthesis of imine XXVI, and 1.01 g (3.5 mmoles) of dimethyl acetylene dicarboxylate in 20 ml of absolute toluene was boiled for 8 h. The solvent was evaporated and the residue (1.76 g) was chromatographed on silica gel (eluent = 1:5 ethyl acetate/pentane) to give 0.3 g of compound XXX as pale yellow crystals.

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BENZIMIDAZOLYLALKYLSULFONIC ACIDS: SYNTHESIS AND ANTIVIRAL PROPERTIES

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Viral diseases are recognized as causing intense harm to the health of people with considerable damage to the national economy, which makes the question of chemotherapy of viral infections one of the most urgent topics of modern virusology [1].

As well as viral influenza infections, other contagious diseases of the respiratory tract, induced by RNA-containing viruses, also occupy a leading place with respect to frequency of occurrence and their epidemic proportions. For a long time the arsenal of specific influenza prophylaxis was filled by various vaccines. However, because of the antigenic mutability of the influenza virus, the use of vaccines appears to be only slightly effective in the dynamics of the epidemic process. This gives a special importance and definite attractiveness to the production of chemotherapeutic agents against influenza infection. To achieve this it is very important to study the manifestations of antiviral properties among various classes of chemical compounds with prospects of further directed search for effective antiviral preparations [3].

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