SYNTHESIS AND PHYSIOLOGICAL ACTIVITY OF 2,3,6-TRIARYL-4-OXO[HYDROXY, HYDROXYIMINO, AMINO]PIPERIDINES

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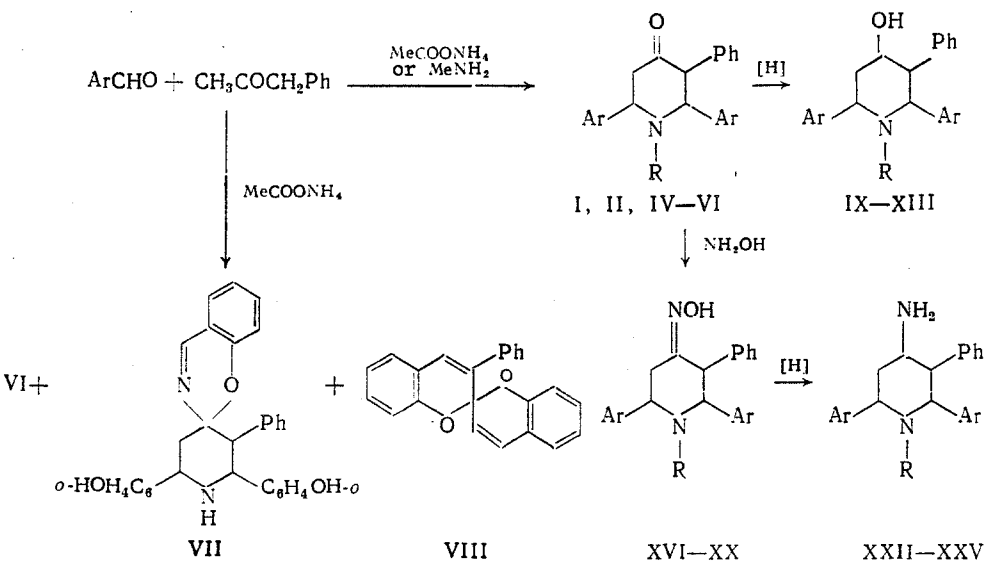
The synthesis and examination of the steric structure and physiological activity of γ-piperidones and γ-piperidols have been the subject of many reports [8, 10, 12]. There is, however, little information on 4-oxo(hydroxy, amino)piperidines with aryl substituents in the α,α',β-positions. A modified Mannich reaction [9, 11, 13] has been used to obtain some novel 3-phenyl-2,6-diaryl-4-oxopiperidines. Benzaldehyde, p-bromo-, and para-methoxybenzaldehyde, and salicylaldehyde have been condensed with methyl benzyl ketone or methyl β-phenethyl ketone and ammonia or methylamine. In order to obtain compounds with bactericidal, fungicidal, and herbicidal activity from γ-piperidones (I, II, IV-VI), their oximes (XVI-XX) and secondary γ-piperidols (IX-XIV) were obtained. The oximes were reduced to the amines (XXII-XXV).

2,3,6-Triphenyl-4-oxopiperidine (I), 2,6-diphenyl-3-benzyl-4-oxopiperidine (III), 3-phenyl-2,6-di-[(p-bromophenyl)- (IV), (p-methoxyphenyl)- (V), and (o-hydroxyphenyl)- (VI)]-4-oxopiperidine were colorless crystalline solids, the constants for which are given in Table 1. The piperidone (II) has been reported previously [9].

It has been reported [11] that the condensation of aliphatic ketones with salicylaldehyde and ammonium acetate in ethanol gives, not the expected α,α'-di-(o-hydroxyphenyl)-4-oxopiperidines, but substituted benzopyrans. On carrying out the analogous condensation of salicylaldehyde with methyl benzyl ketone in acetic acid, in addition to the piperidone (VI) (yield 21%), there was obtained 12-phenyl-9,11-di-(o-hydroxyphenyl)spiro[piperidine-4,2'-(2H-3-aza)chromene] (VII, 22%) and 7-phenyl-2,2'-spirodi-(2H-chromene) (VIII, 39%).



Ar = Ph (I, II, IX, X, XVI, XVII, XXII, XXIII), C_6H_4Br-p (IV, XI, XVIII, XXIV), C_6H_4OMe-p (V, XII, XIX, XXV), C_6H_4OH-o (VI, XIII, XX); R = H (I, IV—VI, IX, XI—XIII, XVI, XVIII—XX, XXII, XXIV, XXV), Me (II, X, XVII, XXIII).

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TABLE 1. Properties of Piperidines Obtained

Compound	Yield, %	mp, °C	IR spectrum, ν_{max}, cm^{-1}	Empirical formula
I	43	161—2	1715, 3317	$C_{21}H_{21}NO$
III	54	92—4	1704, 3313	$C_{23}H_{23}NO$
IV	90	192—3	1720, 3420	$C_{23}H_{19}Br_2NO$
V	48	156—8	1730, 3325, 3420	$C_{25}H_{25}NO_3$
VI	21	157—8	1715, 3300, 3370	$C_{23}H_{22}NO_3$
VII	22	182—3	2460, 2630, 3150 br.,	$C_{30}H_{26}N_2O_3$
VIII	39	153—4	1640	$C_{23}H_{16}O_2$
IX	44	175—6	3312, 3472, 3557	$C_{23}H_{23}NO$
X	37	190—1	3472, 3560	$C_{24}H_{25}NO$
XI	80	128—30	3310, 3350 br.	$C_{23}H_{21}Br_2NO$
XII	100	134—6	3330, 3300 br.	$C_{25}H_{27}NO_3$
XIII	44	179—81	3300, 3370 br., 3480, 3550, 3598	$C_{23}H_{23}NO_3$
XIV	51	173—5	3500	$C_{31}H_{31}NO$
XV	32	106	—	$C_{23}H_{17}N$
XVI	75	195—6	1610, 3280 br., 3340 shoulder	$C_{23}H_{22}N_2O$
XVIII	84	216—8	1662, 3200 br., 3300	$C_{23}H_{20}Br_2N_2O$
XIX	100	199—202	1616, 3260, 3323	$C_{25}H_{26}N_2O_3$
XX	100	185—6	1616, 3250 br., 3400, 3540, 3570	$C_{23}H_{22}N_2O_3$
XXI	31	122	1620, 1730, 3250 br., 3333 br., 3435	$C_{24}H_{24}N_4O$
XXII	80	116—8	3293, 3313, 3380	$C_{23}H_{24}N_2$
XXIII	68	135—7	3290, 3374	$C_{24}H_{26}N_2$
XXIV	82	158—60	3293, 3315, 3380	$C_{23}H_{22}N_2Br_2$
XXV	80	145—6	—	$C_{25}H_{28}N_2O_2$

The structure of the spiro-compound (VII) was confirmed by the presence of five signals for the piperidine ring, together with a singlet at 8.2 ppm attributed to the proton of the azomethine group, and a multiplet of 17 proton units in the aromatic region. The coupling constants between the protons of the piperidine ring show that one of the hydroxyphenyl groups [at $C_{(9)}$] is oriented axially. In the PMR spectrum of the dichromene (VIII), two doublets are seen with coupling constants of 9 Hz for the cis-olefin protons, and a multiplet at 6.8-7.5 ppm with an integral intensity corresponding to the absorption of 14 protons.

The spiro-compound (VII) is apparently formed by condensation of the enol form of the piperidone (VI) with salicylaldimine. Indirect confirmation of this spiroannelation mechanism is provided by the preparation of the spiro-compound (VII) by heating the piperidone (VI) with salicylaldehyde and ammonium acetate in acetic acid, in a separate experiment. The spiro-bichromene (VIII) is formed on condensing two molecules of salicylaldehyde with one molecule of phenylacetone.

The structures of the piperidones (I-VI) were confirmed by their PMR spectra, shown in Table 2. The large values of the vicinal coupling constants (Table 3) for the piperidones indicate that they exist preferentially in the chair conformation, all the aryl substituents being oriented axially [3].

Reduction of the piperidones (I, II, IV-VI) with $NaBH_4$ gave 2,3,6-triphenyl- (IX), 1-methyl-2,3,6-triphenyl- (X), 3-phenyl-2,6-di-[(p-bromophenyl)- (XI), (p-methoxyphenyl)- (XII), and (o-hydroxyphenyl)- (XIII)]-4-hydroxypiperidine, respectively. The piperidone (II) and benzylmagnesium chloride afforded 1-methyl-2,3,6-triphenyl-4-benzyl-4-hydroxypiperidine (XIV). The large values of the vicinal coupling constants for the protons in positions 3, 4, and 5 in the PMR spectra of the piperidols show that the hydroxy groups have the equatorial orientation.

Dehydration and dehydrogenation of the piperidol (IX) by heating with sulfur at 200°C gave 2,3,6-triphenylpyridine (XV). The piperidols (I, II, IV-VI) were converted to the oximes (XVI-XX), which were reduced with sodium in alcohol to the amines (XXII-XXV). According to the PMR spectrum, the amino-group in (XXII) also occupies the equatorial position (Table 2).

Mass spectrometry has provided information on the mode of fragmentation of the triarylpiperidones and their oximes and secondary alcohols which can be used to establish the structures of compounds of this type (Table 4 and Diagram) (see diagram on following page).

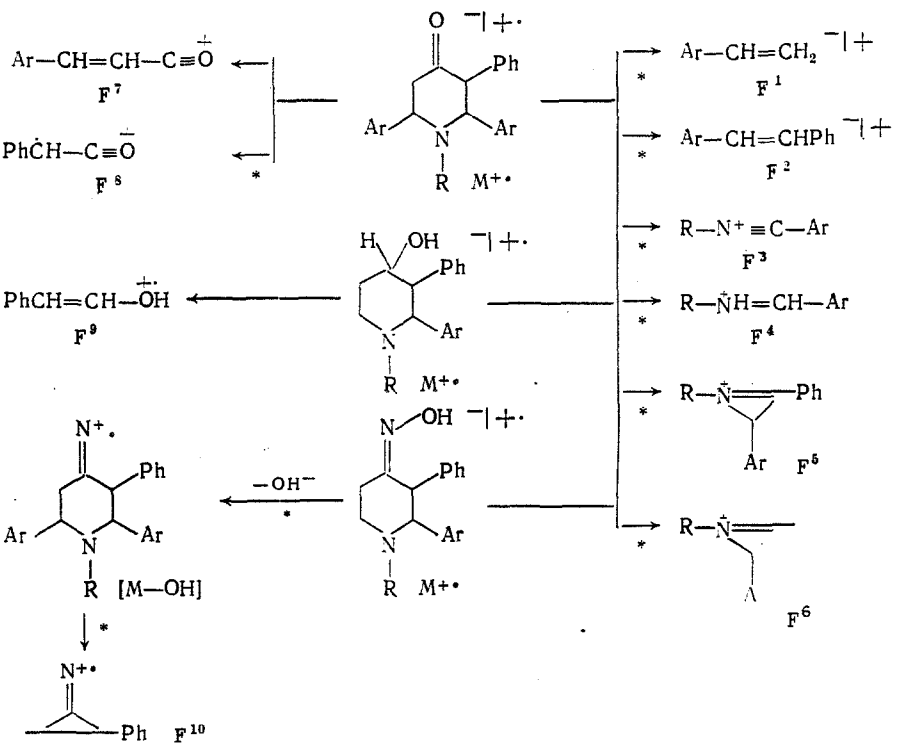
TABLE 2. PMR Spectral Parameters for Piperidines

Compound	Chemical shifts, δ, ppm						
	1-H	2-H	3-H	5-H_a	5-H_e	6-H	other protons
I	2,33	**4,30**	**3,89**	2,94	2,85	4,38	—
IV	2,22	4,19	3,70	2,76	2,76	4,26	—
V	—	4,31	3,93	2,88	2,52	4,27	3,7 and 3,8 (CH_3)
VI	—	4,70	4,37	3,10	2,72	4,64	—
IX	1,76	3,92	2,71	1,81	2,29	4,03	1,76 (OH), 4,12 (4-H)
X	1,76	3,25	2,86	1,80	2,28	3,37	1,51 (OH), 4,11 (4-H)
XI	1,73	3,91	2,64	1,75	2,27	4,00	1,73 (OH), 4,12 (4-H)
XII	1,65	3,83	2,62	1,70	2,22	3,92	1,65 (OH), 4,03 (4-H) 3,65 and 3,7 (CH_3)
XIII	—	4,20	2,85	1,77	2,24	4,24	3,96 (4-H)
XVI	1,70	4,17	3,60	2,13	3,63	4,06	7,68 (OH)
XVII	1,76	3,71	3,50	2,22	3,55	3,41	7,86 (OH)
XVIII	—	4,28	3,70	2,07	3,54	4,05	10,53 (OH)
XIX	—	4,19	3,65	1,99	3,64	3,93	10,48 (OH), 3,63 and 3,74 (CH_3)
XX	—	4,57	3,97	2,10	3,61	4,22	10,7 (OH)
XXII	1,84	3,83	2,41	1,56	2,09	3,96	1,48 (NH_2), 3,13 (4-H)

TABLE 3. Coupling Constants of Piperidines (J, Hz)

Compound	$J_{2_a3_a}$	$J_{3_a4_a}$	$J_{4_a5_a}$	$J_{4_a5_e}$	$J_{5_a5_e}$	$J_{5_a6_a}$	$J_{5_e6_a}$
I, IV—VI	10,6—11,0	—	—	—	13,3—13,7	10,7—12,0	3,5—3,9
IX—XIII, XXII	9,8—10,4	9,8—10,4	10,8—15,0	4,1—4,8	12,0—12,5	11,0—11,5	2,5—3,3
XVI—XX	10,5—11,5	—	—	—	14,1—14,5	8,9—12,2	3,1—3,4

DIAGRAM



The mass spectra of all the compounds obtained showed molecular ion M^+ peaks of high or medium intensity, together with the common ions F^1-F^6 resulting from cleavage of the piperidine ring. Fragments F^1 and F^2 are formed on rupture of bonds $C_{(4)}$—$C_{(5)}$, $C_{(6)}$—$N_{(1)}$, and $C_{(3)}$—$C_{(4)}$, $N_{(1)}$—$C_{(2)}$, respectively, and carry information on the nature of the aryl substituent in positions $C_{(2)}$ and $C_{(6)}$.

TABLE 4. Mass Spectra of (I, II, IV-VI, IX-XIII, XVI-XIX)

Compound	Value m/z (relative intensity, %)											
	M^+	$[M-OH]^+$	F^1	F^2	F^3	F^4	F^5	F^6	F^7	F^8	F^9	F^{10}
I	327	—	104	—	104	106	194	—	131	118	—	—
	(91)		(32)		(16)	(29)	(42)		(9)	(100)		
II	341	—	104	180	118	120	208	—	131	118	—	—
	(27)	—	(8)	(5)	(33)	(44)	(4)	—	(22)	(67)		
IV	483*	—	182*	258*	182*	184*	272*	350*	209*	118	—	—
	(15)		(6)	(3)	(5)	(16)	(12)	(11)	(5)	(100)		
V	387	—	134	210	134	136	224	254	161	118	—	—
	(47)		(80)	(3)	(20)	(37)	(5)	(38)	(41)	(26)		
VI**	359	—	120	196	120	122	210	226	147	118	—	—
	(77)		(9)	(3)	(5)	(45)	(6)	(22)	(31)	(13)		
IX	329	—	104	180	104	106	194	—	—	—	120	—
	(11)		(20)	(8)	(10)	(29)	(100)				(16)	
X	343	326	104	180	118	120	208	—	—	—	120	—
	(45)	(2)	(26)	(15)	(45)	(50)	(4)				(50)	
XI	485*	468*	182*	258*	182*	184*	272*	350*	—	—	120	—
	(15)	(2)	(23)	(4)	(11)	(59)	(37)	(70)			(73)	
XII	389	372	134	210	134	136	224	254	—	—	120	—
	(36)	(1)	(60)	(4)	(40)	(37)	(16)	(66)			(11)	
XIII	361	344	120	196	120	122	210	226	—	—	120	—
	(44)	(3)	(13)	(9)	(13)	(100)	(7)	(87)			(13)	
XVI	342	325	104	180	104	106	194	—	—	—	—	130
	(100)	(28)	(5)	(5)	(5)	(16)	(41)					(13)
XVII	356	339	104	180	118	120	208	—	—	—	—	130
	(56)	(9)	(15)	(7)	(22)	(100)	(5)					(44)
XVIII	498*	481*	182*	258*	182*	184*	272*	350*	—	—	—	130
	(10)	(10)	(20)	(3)	(10)	(79)	(10)	(8)				(100)
XIX	402	385	134	210	134	136	224	254	—	—	—	130
	(64)	(13)	(24)	(3)	(16)	(100)	(6)	(13)				(30)

*Ion peak containing the isotope ^{79}Br shown.
**In addition, the fragment $C_7H_7^+$, m/z 91 (100%) was present.

Ions F^3–F^6 result from amine-type cleavage characteristic of the dissociative ionization of piperidines [1, 2]. These ions enable the type of substituents at the ring nitrogen and positions $C_{(2)}$ and $C_{(6)}$ to be established. Fragmentation of 4-oxopiperidines also results in ketone-type cleavage, characteristic of cyclohexanones [1]. Fission of bonds $C_{(3)}$–$C_{(4)}$ and $C_{(6)}$–$N_{(1)}$, and also $C_{(2)}$–$C_{(3)}$ and $C_{(4)}$–$C_{(5)}$ results in the appearance in the mass spectra of piperidones of the characteristic ions F^7 and F^8. When piperidols undergo dissociative ionization, the fragments $[M - OH]^+$, $[M - H_2O]$, and F^9 are formed.

The mass spectra of the oximes also show peaks for the fragments $[M - OH]^+$, but of much lower intensity than in the case of the piperidols. These ions are further cleaved to give the characteristic fragments F^{10} of moderate and high intensity, which are diagnostic in the mass spectra of the oximes.

The pesticidal activity of the 16 compounds synthesized was examined. They showed no plant growth regulant, insecticidal, or acaricidal activity when tested as described in [4, 6].

The compounds showed low to moderate activity in tests for bactericidal, fungicidal, and herbicidal activity (Table 5). Bactericidal and fungicidal activity was examined in tests on pure cultures of the bacterium Xanthomonas malvacearum and the fungi Fusarium moniliforme and Rhizoctonia solanis, by adding acetone solutions of the compounds to the molten nutrient medium, followed by sowing the microorganisms on the solidified surface [5]. The activity of the compounds was measured as the percentage inhibition of the growth of the microorganisms.

It was found that most of the compounds possessed low bactericidal activity. Moderate activity (50%) was found in 1-methyl-3-benzylpiperidones (II) and the piperidol (XIV), and the 2,3,6-triphenyl-4-oxopiperidine semicarbazone (XXI). Fungicidal activity against the two test organisms in vitro was low, being greatest (38-39%) in the alcohols (XI) and (XIV).

The fungicidal activity of the compounds was also examined on green plants which had been grown to the 6-8 leaf stage, then sprayed with 0.1% suspensions of spores (50-200 thousand/ml) of tomato phytophthora, cucumber powdery mildew, and bean gray mold [5]. Measurements of infection were made on the fourth day in the greenhouse, by the extent of

TABLE 5. Pesticidal Activity of Piperidones (I-VI), (IX-XVII), and (XXI)

Activity and Test Subject	I[c]	II[c]	III[c]	IV	V	VI	IX	X	XI	XII	XIII	XIV	XV	XVI	XVII	XXI
Bactericidal[a]																
Xanthomonas Malvacearum	30	50	30	0	30	10	20	10	30	10	20	50	16	0	0	50
Fungicidal[a]																
Fusarium moniliforme	22	0	33	25	12	0	0	25	38	25	0	39	0	12	25	0
Rhizoctonia solanis	—	—	—	0	25	25	12	0	25	25	12	—	25	25	0	25
cucumber powdery mildew	29	29	19	0	0	0	0	0	0	0	0	0	0	0	0	37
bean gray mold	18	47	29	57	57	57	57	57	57	57	57	0	0	57	57	0
tomato phytophthora	10	8	0	60	33	60	33	60	33	60	60	—	42	60	60	0
Herbicidal[b]																
oats	0	0	0	20	20	20	40	40	40	20	20	—	0	60	40	—
soya	0	0	0	0	20	20	20	0	0	0	0	—	0	0	20	—
radish	10	0	0	40	40	40	60	60	60	40	40	—	0	80	60	—

[a]Percentage inhibition of growth of bacteria, fungal mycelia, or mold given as compared with controls.
[b]Percentage death of germinating plants in vegetative stage shown.
[c]Hydrochlorides.

damage to the leaves (the standards used were euparon, zineb, or polycarbacin at 0.1% concentration). Cucumber powdery mildew showed little sensitivity to any of the test compounds. Significant toxicity was shown by the piperidones (I-III) and the semicarbazone (XXI). However, moderate fungicidal activity was shown by most of the compounds against tomato phytophthora (57%), except the semicarbazone (XXI) and the alcohol (XIV). The methoxy- and hydroxyphenylpiperidols (XII) and (XIII), and both of the oximes examined (XVI, XVII) showed increased activity (60%) against bean gray mold. Considerable inhibition of the development of this disease was observed on treatment with the piperidones (IV) and (VI), having bromo- and hydroxyphenyl-radicals.

Herbicidal activity was examined in the greenhouse on sod-podzolic soil in oats, soya, and radish at the 1-2 leaf stage [7]. The dose rates of the test compounds and the standards were 5 kg active ingredient per hectare. The standards used were Basagran, Dual, and Merpelan. Herbicidal activity was expressed as a percentage of the controls 15 days after treatment of the plants.

The triphenylpiperidones (I-III) were found to be devoid of phytotoxicity. Introduction of bromine, methoxy, or hydroxy-groups into the phenyl substituents (piperidones IV-VI) gave rise to herbicidal activity (20-40%). Reduction of the piperidones to the alcohols also increased herbicidal activity, especially when phenyl and bromophenyl substituents were present. The greatest phytotoxicity was shown by the oximes.

The acute toxicities of (I, II, IV, V, IX-XIII, XVI-XIX, and XXIII) were determined, the LD_{50} values of most of these lying between 800 and 1000 mg/kg. The amine hydrochloride (XXIII) showed high toxicity, its LD_{50} being 56 mg/kg, deaths of the mice occurring following clonic convulsions in the first 5-15 minutes. In tests for activity on the central nervous system, the piperidone (I) and the piperidol (XIV) showed a weak stimulant effect. The remaining compounds showed no sedative, stimulant, or antidepressant activity.

EXPERIMENTAL

PMR spectra were obtained on a Bruker WP-80 spectrometer (TMS) in $CDCl_3$, and mass spectra on an LKV-2091 with an ionizing voltage of 70 eV. IR spectra were recorded on a UR-20 spectrometer in KBr disks. The elemental analyses were in agreement with the calculated values.

3-Phenyl-2,6-diaryl-4-oxopiperidines (I, IV-V). A solution of 0.5 mole of methyl benzyl ketone, 1 mole of the aromatic aldehyde, and 0.5 mole of ammonium acetate in 60 ml of glacial acetic acid was kept for 15 h at 20°C. The resulting crystals were filtered off, washed with 50 ml of ethanol, and crystallized from hexane or benzene. Similarly, from methyl

β-phenethyl ketone and benzaldehyde there was obtained the piperidone (III), and from methyl benzyl ketone, benzaldehyde, and methylamine, the piperidone (II). The hydrochlorides of the piperidones (I-III) had m.p.'s 203-204, 175-177, and 201-203°C, respectively.

3-Phenyl-2,6-di-(o-hydroxyphenyl)-4-oxopiperidine (VI), 12-Phenyl-9,11-di-(o-hydroxyphenyl)spiro[piperidine-4,2'-(2H-3-aza)chromene] (VII), and 7-Phenyl-2,2'-spirodi-(2H-chromene) (VIII). A solution of 67 g (0.5 mole) of methyl benzyl ketone, 122 g (1 mole) of salicylaldehyde, and 77 g (1 mole) of ammonium acetate in 30 ml of ethanol and 60 ml of acetic acid was heated to the boil, then kept for 100 h at 20°C. The solid which separated (154 g) was filtered off and recrystallized from acetone to give 37.7 g of the piperidone (VI). The mother liquors were evaporated, and the residue crystallized from dimethyl sulfoxide to give 50.8 g (22%) of the spiro-compound (VII) as colorless crystals, mp 182-183°C, M^+ 462. $C_{30}H_{26}N_2O_3$. M 462. PMR spectrum (DMSO), δ, ppm: 8.36 s (H^6), 7.46-6.16 m (17H, aromatic protons), 4.41 t (H^9, J 3.2 Hz), 4.21 d (H^{11}, J 11.5 Hz), 3.52 d (H^{12}, J 11.5 Hz), 2.82 and 1.98 d.d (H^{8a},^{8e}, J 13.0 and 3.2 Hz). IR spectrum, ν_{max}, cm^{-1}: 2460, 2630 ($\overset{+}{N}H_2$), 3150 br. (OH), 1637 (C=N). The residue from the mother liquors was chromatographed on alumina (h = 130 cm, d = 0.4 cm, eluent ether–hexane, 1:1) to give 48 g (29.6%) of (VIII) as bright yellow crystals, mp 153-154°C (from hexane). M^+ 324. $C_{23}H_{16}O_2$. M 324. IR spectrum, ν_{max}, cm^{-1}: 1640 (C=C). PMR spectrum, δ, ppm: 7.50-6.80 m (14H, aromatic protons), 6.80 d and 5.76 d (H^{14} and H^{13} cis, J 9 Hz).

A mixture of 0.5 g (1.4 mmole) of the piperidone (I), 4.67 g (38 mmole) of salicylaldehyde, and 1.5 g (19.5 mmole) of ammonium acetate in 3 ml of glacial acetic acid and 10 ml of ethanol was heated on the water bath with stirring for 15 min. The precipitate which separated on cooling was filtered off, washed with water, alcohol, and ether, and dried to give 0.18 g (28%) of a compound which was identical in its melting point, elemental analysis, and spectral properties with the spiro-compound (VII).

3-Phenyl-2,6-diaryl-4-hydroxypiperidines (IX-XIII). To a solution of 15.3 mmole of the piperidone in 100 ml of ethanol was added portionwise with stirring 26 mmole of $NaBH_4$. The mixture was kept for 1 h at 20°C and 20 min at 50°C, then poured onto ice. The solid which separated was filtered off and crystallized from acetone.

1-Methyl-2,3,6-triphenyl-4-benzyl-4-hydroxypiperidine (XIV) was obtained from benzylmagnesium chloride (prepared from 0.09 mole of benzyl chloride and magnesium in dry ether), in 51% yield. Colorless crystals, mp 174-175°C (from acetone), M^+ 433. $C_{31}H_{31}NO$. IR spectrum, ν_{max}, cm^{-1}: 3500 (OH).

2,3,6-Triphenylpyridine (XV). A finely ground mixture of 0.5 g (1.5 mmole) of the piperidol (IX) and 0.33 g (10.2 mmole) of crystalline sulfur was heated for 1 h at 200°C, then cooled and extracted with 50 ml of ether. The residue from the extract was purified on a column of alumina, eluent heptane–ether, 3:1. The pyridine base was obtained as light yellow prismatic crystals.

2,3,6-Triaryl-4-oxopiperidone Oximes (XVI-XX). A solution of 15.3 mmole of the piperidone and 22 mmole of hydroxylamine hydrochloride in 40 ml of ethanol was heated for 3 h at 85°C. The mixture was cooled, treated with sodium carbonate to pH 8.0, boiled for 1 h, and cooled. The crystals which separated were filtered off, washed with water, alcohol, and ether, and dried to give the oximes (XVI-XX).

2,3,6-Triphenyl-4-oxopiperidine Semicarbazone (XXI). To a solution of 2 g (6.12 mmole) of the piperidone (I) in 50 ml of ethanol was added 2 g (18 mmole) of semicarbazide hydrochloride and 3 g of sodium acetate. The mixture was heated with stirring on the water bath for 15 min, and the crystals which separated on cooling were filtered off, washed with water, and dried in vacuo to give 0.72 g (30.6%) of the semicarbazone (XXI) as pale yellow crystals, mp 122°C (from ethanol), M^+ 384. $C_{24}H_{24}N_4O$. M 384. IR spectrum, ν_{max}, cm^{-1}: 1620 (C=N), 1730 br. (C=O), 3250 br. (NH_2), 3333 br. (piperidine NH), 3435 (NH).

2,3,6-Triaryl-4-aminopiperidines (XXII-XXV). To a boiling solution of 11.7 mmole of the piperidone oxime in 35 ml of absolute ethanol was added portionwise 26 g of sodium. The mixture was boiled for 3 h, part of the alcohol distilled off, 150 ml of water added, and extracted with ether. Crystallization of the residue from ethanol gave the aminopiperidines (XXII-XXV).

The properties of the compounds obtained are given in Table 1.

LITERATURE CITED

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α-OXOTHIOHYDROXIMATE S-ESTERS. PREPARATION AND PHYSIOLOGICAL ACTIVITY

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The synthesis of thiohydroximate esters has opened up a new pathway to central cholinesterase reactivators [1, 2, 4, 5, 7]. A distinguishing feature of this approach is that the thiohydroximate esters offer extensive possibilities for the goal-oriented construction of novel molecules with a given type of physiological activity, namely cholinesterase reactivators. If the thiohydroximate ester molecule is arbitrarily split into acid and ester moieties, the construction of novel molecules can be carried out in two main directions, viz., introduction of changes into the structure of the acid or the ester part of the molecule.

The acid components can be hydroximoyl chlorides of the most diverse structure (aliphatic, aromatic with a variety of substituents in the benzene ring [1, 5, 8], and heterocyclic [2, 7]).

The ester component can be provided by aminothiols of different types, or aminoalcohols, to give the corresponding thiohydroximate or hydroximate esters:

$RC(=NOH)Cl + HA(CH_2)_nNR'_2 \rightarrow RC(=NOH)A(CH_2)_nNR'_2 \cdot HCl$, where R is alkyl, aryl, or hetaryl; NR'_2 is a dialkyl or cycloalkylamino-group; A is S or O, and n = 2, 3, 4, or more.

In order to develop further this approach to the generation of novel central cholinesterase reactivators using α-chloro-α-oximinoketones as the hydroximoyl chlorides, we have prepared the α-oxothiohydroximate esters [3] of general formula:

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