the optical densities at λ 613 nm in H_2SO_4—DMSO solutions and at λ 629 nm in H_2SO_4—AcOH solutions. The initial concentration of I was $1 \cdot 10^{-5}$ M.

The electronic absorption spectra were recorded with a Specord UV-vis spectrophotometer.

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SYNTHESIS AND PROPERTIES OF 1,2,2,6,6-PENTAMETHYL-3,5-DIMETHYLENE-4-PIPERIDONE

A. M. Belostotskii and A. B. Shapiro

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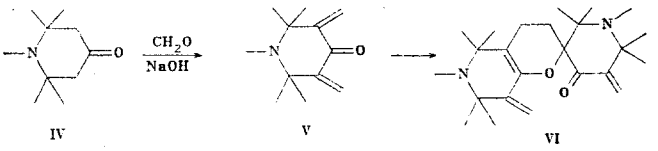
1,2,2,6,6-Pentamethyl-3,5-dimethylene-4-piperidone was synthesized, whereas analogous compounds in the 4-piperidone series could not be isolated. An unusual reaction of the compound obtained with primary aliphatic amines, consisting of successive addition of the amine at the C=C bonds, with a possible formation of an intermediate bicyclic adduct and further elimination of methylamine, was detected.

The reaction of 4-piperidones with formaldehyde has been described in cases of 1,2,5-trimethyl-4-piperidone (I) (the 3-hydroxymethyl derivative was produced) [1], 2,2,6,6-tetramethyl-4-piperidone and its N-oxide (a product of diene synthesis is immediately formed from the unstable bis-adduct by crotonic condensation) [2, 3].

We studied the interaction of 4-piperidones with formaldehyde under conditions of strongly alkaline catalysis (1 N NaOH solution) on the examples of 1-methyl-4-piperidone (II), tropinone (III), and 1,2,2,6,6-pentamethyl-4-piperidone (IV). It was found that only the piperidone IV gives a stable crotonic condensation product V. The corresponding product of diene synthesis VI is formed at an appreciable rate from the unsaturated ketone V only at temperatures above 110-120°C.



IV V VI

The piperidones I-III form polymer reaction products; the condensation of the ketones I and II is accompanied by reduction of the carbonyl group to a hydroxyl by excess formaldehyde (the absence of the carbonyl absorption bands in the region of 1660-1740 cm^{-1} in the IR spectra of the reaction products; the absorption bands of C=C bonds in the region of 1620-

Scientific-Research Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow 125315. Institute of Chemical Physics, Academy of Sciences of the USSR, Moscow 117977.

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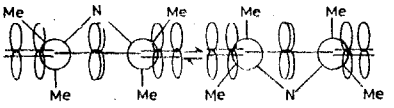
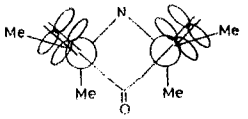
1680 cm^{-1} are also absent). The bicyclic piperidone III is converted to a polymer containing C=O groups (intense bands 1690 cm^{-1} in the IR spectrum) and not possessing C=C bonds (according to the IR spectrum).

The stability of the dimethylene ketone V under conditions of condensation is evidently a consequence of the greatest shielding of the reaction site in the 2,2,6,6-tetrasubstituted system in the series of 4-piperidone derivatives under discussion. The relative inertness of compound V in the Diels–Alder reaction is evidently explained by a further increase in the shielding influence of the α-methyl groups as a result of their steric interaction with the voluminous N-methyl group in comparison with the nitroxyl group [the pressor effect of the N-methyl group hinders the mutual approach of the α-methyl groups of the diene and the carbonyl (activating) group of the dienophile in the formation of the intermediate complex].

The positions of the carbonyl absorption bands in the IR and UV spectra (Table 1) are evidence of the presence of conjugation of the C=C and C=O bonds in compound V, which is confirmed by the bathochromic shift of the band of the π-π^* transition in the UV spectrum with increasing polarity of the solvent. On the basis of this, a partially planar structure A can be ascribed to the piperidone V (all the carbon atoms of the ring lie in the same or almost the same plane). In the structure of A, in addition to the stabilization of its conjugation, there is no repulsion of the olefinic protons and the protons of the α-methyl groups (which increases on account of the pressor effect of the N-methyl group) in comparison with the alternative chair structure B. And yet, structure A should possess supplementary stress as a result of the deviation from a stable conformation of olefins with a shielded double bond.



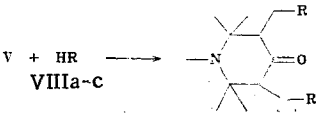
A



B

The presence of one singlet of the protons of the α-methyl groups in the PMR spectrum of the piperidone V is an indication of inversion of the nonplanar portion of the ring. The olefinic protons are nonequivalent in pairs regardless of the degree of degeneracy of the inversion of the flat part of the ring. Reduction of the ketone V by sodium borohydride under mild conditions leads to an entirely saturated product – 1,2,2,3,5,6,6-heptamethyl-4-piperidol (VII) (the absorption of the C=O and C=C bonds is absent in the IR spectrum); moreover, two isomers in a 3:2 ratio are detected by the method of gas–liquid chromatography. Anomalous reduction by sodium borohydride, usually inert with respect to C=C bonds (including the case of unsaturated ketones [4]), indicates a strong activation of the C=C bonds in compound V, which confirms the stress of structure A.

The dimethylene ketone V quantitatively adds secondary amines that have no α-branching. Thus, diisopropylamine and 2,6-dimethylpiperidine do not interact with the ketone V, while the amines VIIIa-c react very rapidly (disappearance of the signals of the olefinic protons in the PMR spectrum and the absorption bands of the C=C bonds in the IR spectrum of the adducts).



IXa-c

IXa: R = aziridino, b: R = morpholino, c: R = piperidino

The reaction with primary aliphatic amines proceeds differently. Although the unsaturated ketone V immediately adds ethylamine Xa analogously to secondary amines, the interaction with sterically hindered amines Xb and c occurs at a 1:1 mole ratio of the reagents and represents a process of successive addition of the initial amine and elimination of methylamine from the original piperidine ring with the formation of new 4-piperidones XIb, c and the accompanying 1-methylpiperidone XIe, the yield of which is 27 and 33%, respectively (the degree of purity of the latter is 90-95% according to the data of gas–liquid chromatography). The formation of the piperidone XIe is the result of an analogous reaction of addition-elimination with

TABLE 1. 1,2,2,6,6-Pentamethyl-3,5-dimethylene-4-piperidone (V) and Its Conversion Products VI, VII, IXa-c, and XIa-d

Compound	mp, °C	IR spectrum, ν, cm^{-1}		UV spectrum		M^+, m/z	Found, %			Gross formula	Calculated			Yield, %
		C=O	C=C	λ_{max}, nm	ε		C	H	N		C	H	N	
V	17	1690	1610, 1618	242[a], 252	11 000 7 500	193	74,3	9,9	7,3	$C_{12}H_{19}NO$	74,2	9,9	7,4	80—85
VI	156—157	1715	1612, 1662	250	10 000	386	74,5	9,9	7,2	$C_{24}H_{38}N_2O_2$	74,2	9,9	7,4	24
VII	42—44	—	—	—	—	199	72,2	12,3	6,9	$C_{12}H_{25}NO$	72,4	12,5	7,2	100
IXa	Oil	1715	—	248—254	—	279	68,8	10,6	15,4	$C_{16}H_{29}N_3O$	68,9	10,4	15,1	100
IXb	121—122	1710	—	230	—	367	65,4	10,3	11,1	$C_{20}H_{37}N_3O_3$	65,4	10,1	11,4	100
IXc	72—73	1710	—	230	—	363	72,3	11,2	11,2	$C_{22}H_{41}N_3O$	72,6	11,3	11,6	100
XIa	Oil	1710	—	230	—	283	68,2	11,4	14,6	$C_{16}H_{33}N_3O$	67,9	11,7	14,9	100
XIb	71—72	1680	1625	266	14 600	235	76,4	10,7	5,9	$C_{15}H_{25}NO$	76,6	10,6	6,0	33
XIc	168—169	1672	1624	268	14 400	313	80,3	9,9	4,7	$C_{21}H_{31}NO$	80,5	9,9	4,5	24
XId	Oil	1675	1624	268	13 200	235	76,5	10,7	5,8	$C_{15}H_{25}NO$	76,6	10,6	6,0	54

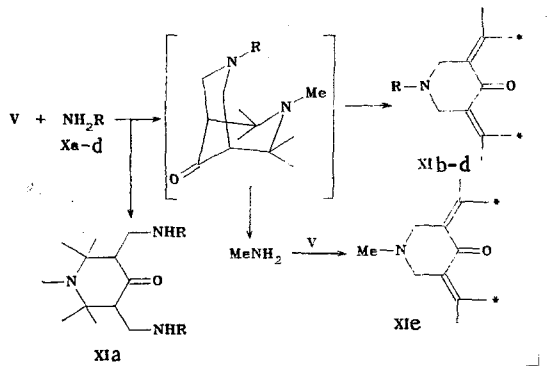
[a]Recorded in alcohol.

TABLE 2. Data of the PMR Spectra of Compounds XIb-e

Compound	δ, ppm (line width, Hz)		
	N-CH_2 of ring	$(CH_3)_2$[a]	$(CH_3)_2$
XIb	3,42	1,97 (4,2)	1,66 (2,4)
XIc	3,48	2,00[a]	1,69[a]
XId	3,25	1,97d (4,2)	1,67 (2,8)
XIe	3,31	2,02 (4,6)	1,68 (2,8)

[a]The signal overlaps with the signals of the other protons.

methylamine gradually liberated in the course of the primary process. Since methylamine is significantly smaller than the voluminous amines Xb and c, and the reaction does not proceed in the direction of simple addition of methylamine to the C=C bonds (just as in the case of the immediately added amine Xa), it can be concluded that for α-unsubstituted primary amines a kinetic control of the reaction is exerted. Thus, the slow addition of n-butylamine Xd and dimethylene ketone V to a large volume of the solvent gives only products of elimination of methylamine XId and XIe (the latter with a 44% yield), whereas when the reagents are poured together, the PMR and IR spectra of the reaction mixture exhibits only a small amount of the piperidone XId together with a predominant amount of another compound, evidently the product of addition of two moles of Xd to the C=C bonds of the ketone V (absence of signals of the olefinic protons in the PMR spectrum; in the IR spectrum the carbonyl absorption band of this product lies at 1710 cm^{-1}).



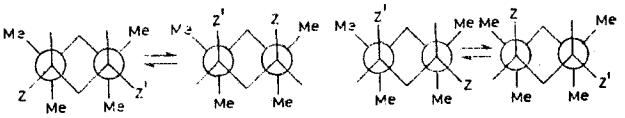
XIa: R = Et, b: R = t-Bu, c: R = 1-adamantyl, d: R = Bu

The reaction pathway under consideration (addition-elimination) is a consequence of the steric peculiarities of the 1,2,2,6,6-pentasubstituted system of the piperidine ring. The intermediate reaction product is symmetrical with respect to elimination of each amine. And yet, the stress that is evidently present in the intermediate product of the reaction and depends on the volume of the substituent R is increased on account of the pressor effect of the N-methyl group. The latter, which also has the reverse effect on the N-methyl group, promotes elimination of methylamine but not of the original amine, the radical R of which does not experience steric pressure on the part of the α-substituents of the ring (hydrogen atoms).

On the basis of the data of the IR and UV spectra, a flattened structure analogous to structure A can be ascribed to the piperidones XIb-e as a result of the presence of conjugation. The PMR spectra of compounds XIb-e also confirm the three-dimensional structure of type A (Table 2). The signal of the protons H* of the two methyl substituents close to the C=O group lies on the weak-field side in comparison with the signal of the other two methyl groups on account of unshielding of the H* protons by the carbonyl. The H* protons are in homoallyl interaction with the N-CH_2 ring protons, which is evident from the substantial broadening of the signal of this pair of methyl groups in comparison with the stronger-field signal of the other pair (analogously to [5]). In the case of the compound XId, the weak-field signal of the pair of methyl groups is a doublet with homoallyl SSCC 1.4 Hz (whereas the second pair gives a narrow signal), which is close to the largest value of homoallyl SSCC [5].

The value of the homoallyl SSCC is a maximum in the case of a perpendicular arrangement of the C–H bonds and the plane of the double bond, which evidently occurs for the N–CH axial protons of the type A structure and is not realized in the type B structure.

The PMR spectra of compounds IXa-c exhibit the presence of two isomers (Table 3). The PMR spectra of each isomer of 1,2,2,6,6-pentamethyl-3,5-disubstituted 4-piperidones IXa-c are characterized by the presence of two singlet signals of the α-methyl groups, which appear as a result of inversion transitions between nonequivalent pairs of axial-equatorial positions of the type $e_Z a \rightleftarrows a_Z e$ (where the subscript Z indicates a skewed conformation of the methyl group relative to the substituent Z, while the absence of a substrate correspondingly indicates a transoid configuration). In view of this, the approximate ratio of cis- and trans-isomers can be estimated according to the integral intensities of the singlets of the α-methyl groups.



The increase in the fraction of one of the isomers with increasing size of the substituent permits us to assume that the predominant isomer is the 3,5-cis-isomer, while the other, correspondingly, is the 3,5-trans-isomer, since the conformational possibility that the substituent Z will be found in a diequatorial position exists for the cis-isomer, whereas one of the substituents Z always has an axial orientation for the trans-isomer (actually, in the case of inversion of the ring the trans-isomer is converted to itself).

EXPERIMENTAL

The UV spectra were recorded on a Perkin-Elmer 402 spectrophotometer (in heptane). The IR spectra were recorded on a Perkin-Elmer 580B spectrophotometer (in tetrachloroethylene); the PMR spectra were recorded on a Varian T-60 spectrometer (in $CDCl_3$; internal standard HMDS). The mass spectra were obtained on a Varian MAT-112 chromato-mass spectrometer (direct input, ionizing voltage 70 eV, temperature of the ionization chamber 100-180°C). Gas-liquid chromatography was conducted on a Tsvet-100 chromatograph (phase SE-30, programming of the temperature 12 deg/min in the interval 100-300°C). For column chromatography we used an RÉPPS-M intermediate recorder (Central Design Office of the Academy of Medical Sciences of the USSR) with UV indication at 260 nm in a Pharmacia SR 25/45 column (column I) and a Pharmacia SR 25/100 column (column 2).

1,2,2,6,6-Pentamethyl-3,5-dimethylene-4-piperidone (V). A mixture of 63 g (0.37 mole) of the ketone IV, 120 ml of a 38% solution of formaldehyde, and a solution of 24 g NaOH in 400 ml of water was shaken for 3 h, extracted with hexane (2 × 100 ml), dried $CaCl_2$, evaporated, and redistilled, collecting the fraction with bp 76°C (0.02 mm). We obtained 60 g of the ketone V. PMR spectrum (CCl_4): 5.90 (2H, d, J = 1.7 Hz); 5.23 (2H, d, J = 1.7 Hz); 2.33 (3H, s); 1.27 ppm (12H, s).

4,5'-Dimethylene-1,1,2,3,3,1',2',2',6',6'-decamethyl-1,2,3,4,7,8-hexahydro-6H-pyrano[3,2-c]pyridine-spiro[6,3']-4'-piperidone; N,N'-dimethylformone (VI). We boiled 1.93 g (0.01 mole) of the ketone V in 3 ml of xylene for 3 h, evaporated, added 20 ml of a 1 N AcOH solution, and chromatographed on an Amberlite IRG-50 cation exchange resin (H^+ form; column 2). It was eluted with a 0-1 N AcOH concentration gradient; the fractions corresponding to the absorption peak were combined, concentrated, a NaOH solution was added to pH 10, and the mixture was extracted with hexane (3 × 30 ml); after recrystallization from hexane we obtained 0.46 g of the dimer VI. PMR spectrum (CCl_4): 5.10 (2H, d, J = 1.7 Hz); 4.84 (2H, d, J = 1.7 Hz); 1.87 (4H, broad signal); 2.28 (6H, s); 1.27, 1.23, 1.21, 1.13, 1.06, 0.96, 0.93, 0.72 ppm (24H, 8s).

1,2,2,3,5,6,6-Heptamethyl-4-piperidol (VII). To a solution of 1.13 g (5.9 mmoles) of the ketone V in 20 ml of a mixture of 50% alcohol at 0-5°C we added a solution of 0.22 g $NaBH_4$ in 10 ml of the same mixture over 20 min, mixed for 1 h at 20°C, and added 10 ml of 50% aqueous acetic acid with cooling. The alcohol was distilled off (the pH of the aqueous solution was adjusted to 10 with NaOH), extracted with chloroform (3 × 50 ml), evaporated, dissolved in hexane, and filtered; after evaporation of the filtrate, 1.16 g of the alcohol VII was obtained.

TABLE 3. PMR Spectra of Compounds IXa-c and XIa

Compound	δ, ppm				Ratio of cis- and trans-isomer
	$(CH_3)_2$	N—CH_3	—CH_2 of ring	O—CH_2	
cis-IXa	0,83; 1,08	2,20	1,42 (t)	—	2 : 1
trans-IXa	0,50; 1,34	2,26	0,95 (t)	—	
cis-IXb	0,80; 1,06	2,23	2,44 (t)	3,66 (t)	19 : 1
trans-IXb	0,70; 1,23	—[a]	—[a]	—[a]	
cis-IXc	0,83; 1,10	2,26	2,40	—	25 : 1
trans-IXc	0,70; 1,17	—[a]	—[a]	—	
cis-XIa	0,84; 1,03	2,22	—	—	3 : 2
trans-XIa	0,61; 1,22	2,28	—	—	

[a]The signal overlaps with the signals of the other protons.

1,2,2,6,6-Pentamethyl-3,5-diaminomethyl-4-piperidones (IXa-c, XIa). To a solution of 10 mmoles of the ketone V in 5 ml of alcohol we added 21 mmoles of the amines VIIIa-c, Xa; after evaporation (bath temperature <40°C) we obtained the piperidones IXa-c and XIa.

1-Alkyl-3,5-diisopropylidene-4-piperidones (XIb-d). To a solution of 5 mmoles of the ketone V in 3 ml of alcohol we added 5.1 mmoles of the amine Xb, c, evaporated after 24 h, and chromatographed on neutral Al_2O_3, II-III degree of activity (column 1, eluting successively with petroleum ether and chloroform). The mixture was chromatographed on silica gel (column 1, eluting successively with 1 liter of a mixture of petroleum ether and ether (4:1) and 1.5 liters of chloroform); the piperidones XIb, c were obtained from the fraction of the first eluate after evaporation, and the piperidone XIe from the fraction of the second eluate.

A solution of 0.23 g (1.2 mmoles) of the ketone V in 50 ml of alcohol and a solution of 0.17 g (2.4 mmoles) of the amine XId in 50 ml of alcohol was added simultaneously to 0.5 liter of alcohol over a period of 15 h, left for 24 h, and after evaporation and analogous chromatographic separation, we obtained 0.15 g of the piperidone XId and 0.11 g of the piperidone XIe. IR spectrum of compound XIe: 1625 (C=C), 1675 cm^{-1} (C=O). UV spectrum: λ_{max} 268 nm, $\varepsilon \sim 14{,}000$. M^+ 193.

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