NUCLEOPHILIC ADDITION TO 1,2,2,6,6-PENTAMETHYL-3,5-DIMETHYLENE-4-PIPERIDONE

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Like branched primary amines, unbranched mercaptans react with 1,2,2,6,6-pentamethyl-3,5-dimethylene-4-piperidone to give products of ring opening. On the basis of the data obtained, a reaction scheme that includes the intermediate formation of 3,7-diazabicyclo[3.3.1]nonan-9-one seems less likely as compared with a scheme involving elimination from the monocyclic piperidine system. It is also shown that steric interaction of the vicinal substituents is one of the important factors that promote β elimination.

The specific differences in reactivities that are associated with the presence of a large number of sterically interacting substituents (except for the ability to form stable nitroxyl radicals) have not been noted in reviews on the chemistry of 4-piperidones [1] and polysubstituted piperidines [2]. The existence of such peculiarities, particularly opening of the piperidine ring during its acylation [4], has been pointed out for the tetrasubstituted system of triacetoneamine and its derivatives [3]. We recently observed that both normal products of β amination (pathway A) and unusual products of opening and closing of the piperidine ring (pathway B) are formed in the addition of amines to 1,2,2,6,6-pentamethyl-3,5-dimethylene-4-piperidone (I) [5]. In this connection, in the present research we continued our study of the chemical properties of polysubstituted piperidone I.

To precisely determine the effect of the structure of the aliphatic amine on the character of the reaction with dimethylene ketone I we used β-substituted amines IIa-c (primary and secondary) and α-branched primary amine IId. Amines IIa-c give reaction products that are formed via pathway A – substituted triacetoneamines IIIa-c. The reaction with amine IId proceeds via pathway B and gives a product of addition of the amine – splitting out of methylamine (IVa) – together with a product of the same reaction with the liberated methylamine – piperidone IVb. Thus β substitution in secondary amines does not hinder addition to the C=C bonds of dimethylene ketone I (in contrast to α substitution [5]). In the case of branching in the α position of primary amines, regardless of tertiary [5] or secondary character of the α-carbon atom of the amine, the rate of the reaction via pathway B proves to be quite high. Substitution in the β position of primary amines evidently does not have a strong effect on the primary realization of pathway A. (See Scheme I).

Compounds IIIa-c are formed as mixtures of the cis and trans isomers with preponderance of the former (Table 1; here and subsequently, the isomer ratios were determined from the integral intensities of the signals of the geminal methyl groups in the PMR spectra). The assignment of the signals of the isomers was made as in [5]. The existence of conjugation of the C=C and C=O bonds in enone IVa (on the basis of the IR and UV spectra) indicates that this ring exists in a conformation that is close to a half boat; this was previously noted for piperidone IVb [5].

The occurrence of the reaction via pathway B can be represented by two schemes: 1) addition of the amine to one C=C bond; 2) β elimination (ring opening on the side of the added amine) [for 2*) addition of the alkylamino group to the second C=C bond with the formation of a bispidone]; 3) addition of the alkylamino group to the second C=C bond (recyclization) [or 3*) β elimination of the methylamino group]; 4) β elimination of methylamine. On the basis of general sterochemical concepts it is difficult to draw any conclusions regarding the realization of the sequence of steps 1–2–3–4 or 1–2*–3*–4. The possibility of ring opening in step 2 can be explained by an increase in the energy of the system as a result of compression of the six-membered ring. In the second case one cannot exclude decomposition of the interme-

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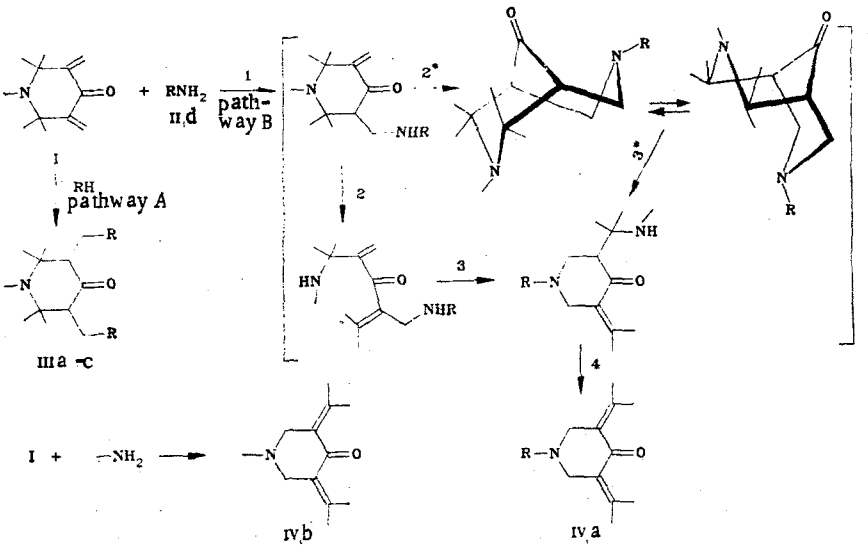
TABLE 1. Products of the Transformations of Substituted Piperidones IIIa-c, IVa, Va-c, VII, VIII, X, and XIa,b

Compound	Isomer ratio	mp, °C	IR spectrum, ν, cm^{-1}		UV spectrum, λ_{max}, nm	M^+, m/z	Found, %				Empirical formula	Calculated, %				Yield, %*
			C=O	C=C			C	H	N	S		C	H	N	S	
IIIa	15:1	Oil	1710	—			69,0	8,6	7,6	—	$C_{28}H_{49}N_3O_5$	69,3	8,8	7,5	—	100
IIIb	15:1	Oil	1710	—			70,0	10,8	16.4	—	$C_{26}H_{49}N_5O$	70,1	10,7	15,7	—	100
IIIc	4:1	Oil	1710	—			77,0	9,6	9,7	—	$C_{28}H_{41}N_3O$	77,3	9,4	9,8	—	100
IVa	—	111—112	1675	1625		313	80,4	9,9	4,6	—	$C_{21}H_{31}NO$	80,5	9,9	4,5		30(28)
Va	—	Oil	1660	1620	250	319**	56,2	8,3	—	20,2	$C_{15}H_{26}O_3S_2$	56,6	8,2	—	20,0	81(7)
Vb	—	Oil	1660	1620	250	452**	71,4	10,6	—	14,1	$C_{27}H_{48}OS_2$	71,7	10,6	—	14,2	75
Vc	—	45—55	1655	1600	255	513**	60,7	7,9	—	24,6	$C_{26}H_{40}O_2S_4$	61,0	7,8	—	25,0	32
VII	3:1	Oil	1700	—		336**	53,7	8,8	4,4	19,3	$C_{15}H_{29}NO_3S_2$	53,8	8,7	4,2	19,1	100
VIII	—	205 dec.	1710, 1720	—		—	42,0	7,0	4,7	—	$C_{11}H_{22}INO$	42,5	7,1	4,5	—	66
X	1,7:1	90—92	1734	—		225	63,7	8,6	6,0	—	$C_{12}H_{19}NO_3$	64,0	8,4	6,2	—	43
XIa	2:1	68—70	1725, 1740	—		268**	67,4	9,3	5,2	—	$C_{15}H_{25}NO_3$	67,5	9,4	5,2	—	100
XIb	3:1	119—120	1730, 1740	—		346**	72,9	9,1	4,2	—	$C_{21}H_{31}NO_3$	73,0	9,0	4,1	—	100

*The yield of amine IIb is given in parentheses.
**The value for the protonated molecular ion $(M + H)^+$ obtained by chemical ionization is indicated.

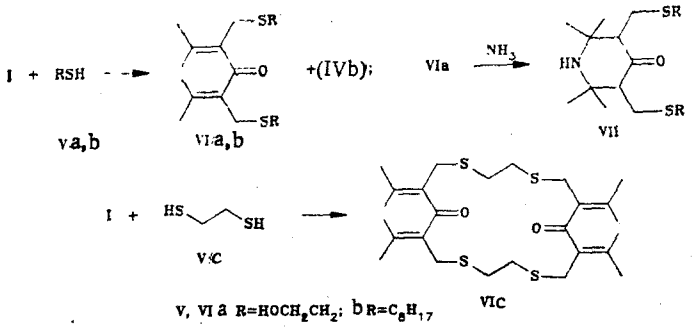


II, III a R= 3-carbethoxypiperidino; b R= octahydropyrrolo[1,2-a]pyrazine; c R= =2-phenylethylamino; d R=2-adamanfyl

Scheme I

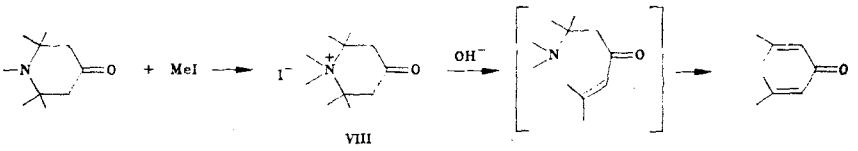
diate bicyclic product of step 2*. Triacetoneamine derivatives are unknown among various polysubstituted 3,7-diazabicyclo[3.3.1]nonan-9-ones [1, 6]. In addition, a chair–boat conformation is characteristic for bispidones, and the barrier to interconversion of the component rings is quite low [7]. As a consequence of this, an increase in the strain in the polysubstituted piperidine ring of the intermediate 3,7-diazabicyclo[3.3.1]nonan-9-one is possible because of eclipsing of the four alkyl substituents in the boat conformation, as well as a result of the pressor effect of the N-methyl group.

Data obtained in a study of the reaction of dimethylenepiperidone I with mercaptans Va-c provide evidence in favor of the first scheme. Ring-opening products VIa-c are formed; in the first case a product of an accompanying reaction with the liberated methylamine – piperidone IVb –is also formed. Since a bicyclic adduct cannot be formed at all in this case and elimination of methylamine was observed, it may be assumed that the reaction of dienone I with mercaptans proceeds in accordance with the first scheme. The reverse closing of substituted phorons VIa to ring VII with ammonia shows that opening of the chair 3,5-disubstituted piperidine ring hardly occurred (in the first scheme elimination occurs from the compressed ring).



The first β elimination (step 2) is a consequence of different cyclic strains in the partially compressed monocyclic adduct of step 1, which increase because of steric interaction of the vicinal substituents. Nevertheless, it is not possible to consider the contribution of strictly this interaction, i.e., the contribution of torsion strain to the overall increase in the energy of the system, to be the principal one. In the case of the second β elimination (step 4) the methylamino group that is split out does not enter into the composition of the ring, and the nonbonding interaction of the vicinal substituents proves to be the only steric factor that promotes β elimination in β-amino ketones.

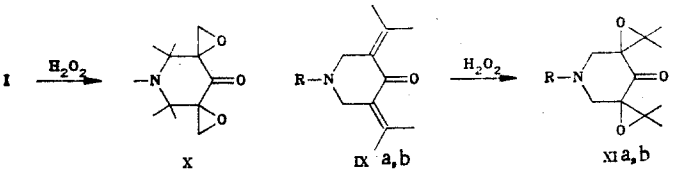
The observed formation of phorone in the alkaline treatment of methiodide VIII at 20°C serves as a confirmation of this pressor effect. The acyclic product of Hofmann degradation proves to be unstable, and the α,α-disubstituted dimethylamino group is eliminated (evidently in the form of dimethylamine). 1-Methyl-4-piperidone methiodide does not undergo Hofmann degradation at all under the same conditions. Tropinone methiodide, being an α,α'-disubstituted piperidone, gives products of elimination of dimethylamine – a mixture of isomeric cycloheptadienones [8]. The alkaline decomposition of methiodides of 2-substituted 4-piperidones stops after Hofmann ring opening; the ring opens on the side of the α-substituted carbon atom [9]. Acyclic N-methyl- and N,N-dimethyldiacetoneamines (like cyclic triacetoneamines IIIa-c) decompose to the starting components at elevated temperatures [10].



Steric requirements are responsible for the s-trans-s-trans conformation of sulfides VIa-c, in contrast to the s-cis-s-cis conformation of phorone, a conclusion regarding which on the basis of the PMR spectra is not sufficiently rigorous without comparison with the spectra of compounds with known conformations [11]. In the PMR spectra of piperidones IVa,b with a fixed s-cis-s-cis conformation the signals of the two chemically nonequivalent pairs of methyl substituents are markedly spread apart as a consequence of impinging of one pair into the region of magnetic anisotropy of the carbonyl group (which is also observed in the PMR spectrum of phorone [11]). For substituted phorones IVa,c the same nonequivalent methyl groups in pairs give one singlet (two closely located signals for VIb); taking into account the conjugation of the C=C and C=O bonds (from the UV spectra), this indicates an alternative s-trans-s-trans conformation of these compounds.

Piperidone VII is formed as a mixture of cis and trans isomers with threefold preponderance of one of them. The cis isomer is evidently the predominant species (it is the isomer with a more favorable 3,5-diequatorial orientation of the substituents).

For an additional evaluation of the steric requirements of the 1,2,2,6,6-pentasubstituted piperidine system with respect to the orientation of the substituents in the 3 and 5 positions in 4-piperidones we carried out the epoxidation of piperidones I and IXa,b; the formation of 3,5-disubstituted cis or trans isomers was excluded, and their ratio cannot affect the relative amounts of 3,3,5,5-tetrasubstituted isomers. Nucleophilic attack by the peroxide anion at the C=C bond also cannot give rise to opening of the ring via pathway B, since the development of an oxide ring is not accompanied by the addition of a proton in the α position relative to the C=O group. In the case of dienone I we obtained completely substituted piperidone X in addition to a compound with an unestablished structure (according to the IR and PMR spectra, the latter is not an amino carboxylic acid – the product of simple Baeyer–Villiger oxidation).



IX, XI a R=*t*-Bu; b R= 1-adamantyl

Unsubstituted analogs IXa,b give diepoxides XIa,b in quantitative yields in the form of mixtures of isomers in unequal ratios (Table 1). Polysubstituted piperidone X is also a mixture of isomers with a small preponderance of one of them (according to the integral intensities of the OCH_2 protons in the PMR spectrum). The results obtained provide evidence for the low stereoselectivity of the epoxidation of conjugated exocyclic double bonds in 4-piperidones. This is evidently associated with the fact that the geminal substituents in the 3 and 5 positions in the examined spirooxiranes are not purely axial or purely equatorial by reason of the small angle between them in the three-membered ring and thus may prove to be close in conformational energies. It is possible that finding of the signals of the paired nonequivalent gem-methyl groups in the PMR spectrum of diepoxide X is also a consequence of a nonclassical orientation of the substituents in the 3 and 5 positions.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in $CDCl_3$ were recorded with Varian T-60 and Varian HA-100 spectrometers with hexamethyldisiloxane (HMDS) as the standard. The IR spectra of mineral oil suspensions or thin layers of the compounds were obtained with a Perkin-Elmer 580B spectrometer. The UV spectra of solutions in hexane were recorded with a Perkin-Elmer 402 spectrophotometer. The chemical-ionization mass spectra were obtained with a Finnigan 4021 mass spectrometer (NH_3 as the reactant gas, 0.4 torr, 100 eV, heating rate 100°C/min). The electron-impact mass spectra were obtained with a Varian MAT-112 mass spectrometer (direct introduction, 70 eV, 100°C). An RÉPPS-1 flow recorder (Central Design Office, Academy of Medical Sciences of the USSR), with UV indication at 260 nm, and a Pharmacia SR 25/45 column were used for column chromatography.

1,2,2,6,6-Pentamethyl-3,5-bis(alkylaminomethyl)-4-piperidones IIIa-c. A 20-mmole sample of the amine (IIa-c) was added to a solution of 10 mmole of ketone I in 5 ml of alcohol, and the mixture was allowed to stand for 3 h. Evaporation gave the piperidone (IIIa-c). PMR spectrum of piperidone IIIc (here and subsequently, the signals of the preponderant isomer are denoted by an asterisk): 7.40 (10H, broad s); 2.30-3.50 (14H, superimposition of multiplets); 2.27, 2.30* (3H, two s); 1.23, 1.02*, 0.82*, 0.59 ppm (12H, four s).

1-(2-Adamantyl)-3,5-diisopropylidene-4-piperidone (IVa). A solution of 5 mmole of ketone I and 5 mmole of amine IId in 5 ml of alcohol was allowed to stand for 3 days, after which it was evaporated, and the residue was chromatographed on neutral activity II Al_2O_3 (successive elution with hexane and chloroform). The substance isolated from the fractions of the chloroform eluate was chromatographed on silica gel [successive elution with hexane–ether (4:1) and chloroform]. Piperidone IVa was obtained from the fractions of the first eluate after evaporation, while piperidone IVb (identified from the IR and PMR spectra [5]) was obtained from the fractions of the second eluate.

2,6-Dimethyl-3,5-bis(alkylthiomethyl)-2,5-heptadien-4-ones VIa,b and 6,8,15,17-Tetraisopropylidene-1,4,10,13-tetrathiacyclooctadecane-7,16-dione (VIc). A solution of 20 mmole of ketone I in 50 ml of benzene and a solution of 40 mmole of the mercaptan (Va,b) (20 mmole of mercaptan Vc) in 50 ml of alcohol were added in the course of 15 h in an argon atmosphere to 500 ml of benzene, after which the mixture was allowed to stand for 12 h and evaporated.

For the isolation of sulfide VIa the mixture was chromatographed on silica gel [application in chloroform, successive elution with 0.6 liter of chloroform and 0.5 liter of chloroform–alcohol (4:1)], and piperidone IVb was obtained from the fractions of the chloroform eluate after evaporation; heptadienone VIa was obtained from the fractions of the mixed eluate. PMR spectrum of VIa: 3.66 (4H, t, J = 6 Hz); 3.42 (4H, s); 2.60 (4H, t, J = 6 Hz); 1.85 (12H, s); and 1.06 ppm (2H, broad signal).

For the isolation of sulfide VIb the mixture was chromatographed on silica gel [application in hexane, successive elution with 0.3 liter of hexane and 0.7 liter of hexane–ether (4:1)], and heptadienone VIb was obtained from the fractions of the latter eluate after evap-

oration. PMR spectrum: 3.44 (4H, s, SCH_2); 2.47 (4H, t, J = 7.5 Hz, SCH_2); 1.91, 1.89 (12H, two s, Me); 1.56 (4H, quintet, $SC-CH_2-C$); 1.25-1.40 (20H, superimposition of multiplets, CH_2); 0.89 ppm (6H, t, J = 6 Hz, CH_3).

For the isolation of sulfide VIc the mixture was chromatographed on silica gel (application in chloroform, elution with chloroform), and the residue obtained after evaporation was chromatographed on acidic Al_2O_3 (Merck, type T; application in CCl_4, successive elution with 0.5 liter of CCl_4 and 0.5 liter of chloroform); macrocycle VIc was obtained from the fractions of the second eluate after evaporation. PMR spectrum: 3.73 (8H, s); 2.78 (8H, s); and 1.80 ppm (24H, s).

2,2,6,6-Tetramethyl-3,5-bis[(2-hydroxyethylthio)methyl]-4-piperidone (VII). A solution of 20 mmole of substituted phorone VIa was allowed to stand in 20 ml of a concentrated solution of NH_3 in chloroform for 3 months, after which the mixture was evaporated to give piperidone VII. PMR spectrum: 3.75 (4H, t, J = 7 Hz); 2.40-3.50 (10H, superimposition of multiplets); 1.27*, 1.17, 1.04, 0.92* ppm (12H, s).

1,2,2,6,6-Pentamethyl-4-piperidone Methiodide (VIII). A solution of 20 mmole of N-methyl triacetoneamine in 20 ml of methyl iodide was allowed to stand in the dark at 25°C for 6-8 months, after which the precipitated quaternary salt VIII was removed by filtration, washed with hexane, and dried over P_2O_5.

Alkaline Treatment of Methiodide VIII. A solution of 2.5 g of KOH in 5 ml of water was added to a suspension of 3 g (9.6 mmole) of methiodide VIII in 50 ml of water; after 1 h, the resulting precipitate was removed by filtration and dried over KOH to give 0.73 g (55%) of phorone (identified from the PMR spectrum and mp 28°C).

1',2',2',6',6'-Pentamethyl-3'-spiro-2-oxirane-5'-spiro-2"-oxirane-4'-piperidone (X). A 3-ml sample of a 28% solution of H_2O_2 was added dropwise at 15°C to a solution of 1.07 g (11 mmole) of dimethylene ketone I in 20 ml of methanol–water (2:1), after which a solution of 1 g of NaOH in 10 ml of the same mixture was added. After 5 min, 10 ml of water was added, and the mixture was neutralized by bubbling in CO_2. The methanol was removed by distillation, and the residue was extracted with chloroform. The organic phase was dried with Na_2SO_4 and evaporated, and the residue was chromatographed on silica gel (application in chloroform, elution with chloroform); evaporation gave diepoxide X. A 0.32-g sample of a compound with an unestablished structure was isolated from the aqueous phase after evaporation, drying, separation of the inorganic salts with 2-propanol, and chromatography on Amberlit IRG-50 cation-exchange resin. PMR spectrum of diepoxide X: 2.86*, 2.92, (4H, two s); 2.39 (3H, s); 1.12 ppm (12H, s).

1'-Alkyl-3,3,3",3"-tetramethyl-3'-spiro-2-oxirane-5'-spiro-2"-oxirane-4'-piperidones XIa,b. A mixture of 10 mmole of the piperidone (IXa,b) [5], 8 ml of methanol, 1 ml of a 28% solution of H_2O_2, and 0.25 g of KOH in 3 ml of water was allowed to stand overnight, after which the methanol was removed by distillation, and the residue was extracted with hexane–chloroform (9:1). Evaporation gave the diepoxide (XIa,b). PMR spectrum of XIa: 3.12, 3.06 (4H, two AB systems, J = J* = 12 Hz); 1.16 (9H, s); 1.41*, 1.33, 1.27, 1.12* ppm (12H, four s) PMR spectrum of XIb: 3.16, 3.06* (4H, two AB systems, J = J* = 12 Hz); 1.5-2.5 (15H, superimposition of multiplets); 1.41*, 1.30, 1.25, 1.16* ppm (12 H, four s).

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