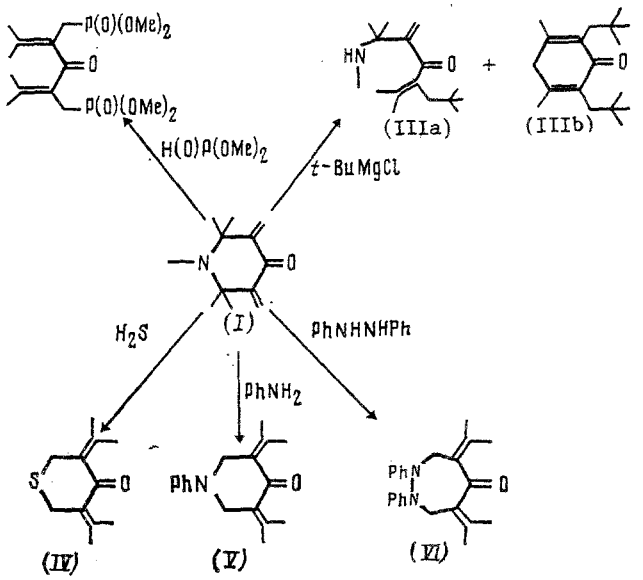
POSSIBLE USE OF 1,2,2,6,6-PENTAMETHYL-3,5-DIMETHYLENE-4-PIPERIDONE IN THE SYNTHESIS OF SATURATED HETEROCYCLES

A. B. Shapiro and A. M. Belostotskii

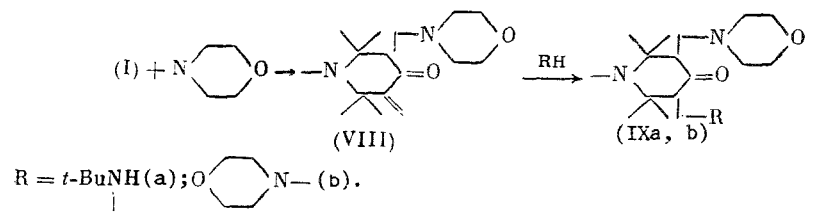
UDC 547.824:542.91:547.818:547.828:547.892

The behavior of 1,2,2,6,6-pentamethyl-3,5-dimethylene-4-piperidone (I) in Michael reactions has been reported in [1-3]. Continuing these studies, we have now examined the possibility of obtaining saturated heterocyclic compounds from the piperidone (I). On reaction with a variety of nucleophiles, the latter either undergoes opening of the piperidine ring, or gives products of subsequent cyclization.

Reaction of (I) with H_2S, aniline, or hydrazobenzene affords the tetrahydrothiopyranone (IV), the N-phenylpiperidone (V), or the hexahydrodiazepinone (VI), respectively. The phorones (II) and (IIIb) do not undergo cyclization to the 4-piperidones on heating to 100°C with ammonia or methylamine under pressure, although phorone reacts quite readily [4]. Less substituted dienones do not react with t-$BuNH_2$ [5]. It has been suggested that the reason for the opening of the piperidine ring in the reaction of (I) with nucleophiles is the instability of the product of addition to a single C=C bond [3]. As expected, under conditions which decrease the reaction rate (greater dilution and slower addition), the reaction of morpholine with (I) gives the stable addition product (VIII). On reaction with t-$BuNH_2$, the latter is converted into the stable piperidone (IXa) as a mixture of cis and trans isomers in approximately equal amounts (as shown by the integral intensities of the signals



for the α-methyl groups in the PMR spectrum).



Institute of Chemical Physics, Academy of Sciences of the USSR, Moscow. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 3, pp. 667-671, March, 1989. Original article submitted November 30, 1987.

0568-5230/89/3803-0593 $12.50

TABLE 1. Yields and Properties of Obtained Compounds

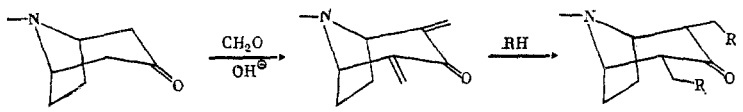
Compound	Yield, %	Mp, °C	IR spectrum, ν, cm^{-1}			Calculated/ Found, %			Empirical formula
			C=C	C=O	NH	C	H	N	
(II)	32	44–46	1620	1675	–	46.8 / 47.1	7.5 / 7.3	–	$C_{15}H_{28}P_2O_7$
(IIIa)	10	Oil	1650	1670	3370	76.2 / 76.5	11.8 / 11.6	5.4 / 5.6	$C_{16}H_{29}NO$
(IIIb)	24	43–46	1620	1670	–	82.2 / 81.9	12.4 / 12.2	–	$C_{19}H_{34}O$
(IV)	63	45	1620	1690	–	67.0 / 67.4	8.2 / 8.2	–	$C_{11}H_{16}OS$
(V)	38	76–77	1620	1680	–	80.2 / 80.0	8.2 / 8.3	5.5 / 5.5	$C_{17}H_{21}NO$
(VI)	90	93–95	1610	1690	–	79.6 / 79.8	6.9 / 7.5	7.8 / 8.1	$C_{23}H_{26}N_2O$
(VIII)	95	Oil	1610	1690	–	68.2 / 68.6	10.3 / 10.0	9.8 / 10.0	$C_{16}H_{23}N_2O_2$
(IXa)	98	101–102	–	1710	3340	67.8 / 68.0	11.0 / 11.0	12.0 / 11.9	$C_{20}H_{39}N_3O_2$
(XI)	25	Oil	1610	1690	–	73.5 / 73.6	7.9 / 7.9	8.7 / 8.6	$C_{10}H_{13}NO$
(XIIa)	97	63–65	–	–	–	71.8 / 72.1	10.7 / 10.5	12.3 / 12.6	$C_{20}H_{35}N_3O$
(XIIb)	75	Oil	–	1710	–	52.2 / 52.6	8.1 / 7.8	4.1 / 4.1	$C_{14}H_{25}NO_3S_2$

On changing the order of addition of the nucleophiles, ring opening occurs as early as the stage of addition of t-$BuNH_2$ to one of the C=C bonds of the dienone (I) [1, 3]. It appears that the conformation of 3-alkylaminomethyl-5-methylene-1,2,2,6,6-pentamethyl-4-piperidones with a partially flattened ring possessing a bulky substituent in the α-position is somewhat strained, resulting in opening of the ring (as shown, in particular, by the formation of the dienone (IIIa), which is the product of the opening of the piperidone ring in (I) following addition of one mole of the bulky nucleophile).

The formation of the 3,5-disubstituted piperidone (IXa) may be due to the greater stability of the chair conformation, even when one bulky substituent is present. Reaction of the enone (VIII) with morpholine gives a quantitative yield of the piperidone (IXb), reported previously [1].

It was also of interest to find whether it was possible to use other substituted 3,5-dimethylene-4-piperidones for the construction of cyclic systems based thereon by similar cleavage–closure of the piperidine ring with nucleophiles. Conditions were found under which condensation of the tropinone (X) with formaldehyde gave the dienone (XI). The latter adds piperidine and 2-mercaptoethanol will give the corresponding tropinones (XIIa, b).

It has been shown that reaction of (I) with mercaptans affords alkylthiomethylphorones [3], related to the dienones (II) and (IIIb). Since mercaptoethanol does not liberate methylamine from the 2,6-disubstituted piperidone (XI), it may be concluded that the observed opening of the piperidone ring in (I) is unique to 4-piperidones. The behavior of this polysubstituted system is due to the increased energy of the latter (as compared with the less-substituted analogs). It appears that the steric energy



(X) (XI) (XIIa, b)

R= (a); $HOCH_2CH_2S$- (b).

of the enones (VIII) increases as a result of the distortion of the ring skeleton as a result of allylic interaction of the geminal α-methyl group with the protons of the adjacent C=C bond ($A^{1,3}$-stress [6]), as well as steric repulsion of the α- and β-alkyl vicinal substituents on the other side of the ring. In conclusion, it may be noted that the similarity of the chemical shifts of the methyl groups at the C=C bonds in the PMR spectra of (II) and (IIIb) indicates [3] that these dienones have the S-trans-S-trans conformation. The properties of the products obtained are given in Table 1.

EXPERIMENTAL

PMR spectra were obtained on a Brucker WP-200 spectrometer, in $CDCl_3$, and IR spectra on a UR-10 spectrophotometer (in thin films or KBr), UV spectra on a Specord UV-VIS spectrophotometer (in heptane), and mass spectra on a Varian MAT-112 mass spectrometer (direct introduction, 70 eV, 120°C). Column chromatography was carried out on a 2 × 1.5 cm column with an REPPS-1M UV recorder (Central Constructional Department, Academy of Medical Sciences of the USSR).

2,4-Diisopropylidenepentan-3-one-1,5-bisdimethylphosphonate (II). A mixture of 0.97 g of (I), 20 ml of methanol, and 1.1 g of dimethyl phosphite was kept at 40°C for 6 h under argon, then evaporated and chromatographed on silica (applied in a 10:1 mixture of hexane and chloroform), and eluted successively with chloroform and a 10:1 mixture of chloroform and ethanol. The compound obtained from the latter eluent was chromatographed on neutral alumina (eluent, chloroform) to give 0.6 g of (II). PMR spectrum (δ, ppm, J, Hz): 1.90 s (6H, MeC=C), 1.93 s (6H, MeC=C), 2.84 d (4H, PCH_2, $^2J_{P-H}$ = 21.9), and 3.72 d (12H, OMe, $^3J_{P-H}$ = 11.0).

2,6-Dimethyl-3-neopentyl-5-(1,1-dimethyl-2-methylaminomethyl)-2,5-hexadien-4-one (IIIa) and 2,6-Dimethyl-3,5-dineopentyl-2,5-hexadien-4-one (IIIb). To a fourfold excess of t-BuMgCl in 10 ml of ether was added at 20°C a solution of 1.15 g of (I) in 10 ml of ether over 5 min. After 5 min, the mixture was treated with ammonium chloride solution, extracted with hexane, dried over Na_2SO_4, and chromatographed on silica, eluting successively with hexane, chloroform, and chloroform–ethanol (5:1). From the latter eluate there was obtained 0.15 g of (IIIa). The product isolated from the first fraction was again chromatographed, and eluted with CCl_4 to give 0.35 g of (IIIb); m/z 278 (M^+). PMR spectrum of (IIIa) (δ, ppm): 0.82 s (9H, t-Bu), 1.20 s (6H, MeCN), 1.58 s (3H, MeC=C), 1.73 s (3H, MeC=C), 2.24 s (3H, NMe), 2.15 s (2H, CH_2), 3.40 br. signal (1H, NH), 5.83 d (1H, CH=C, ^2J = 0.5 Hz), 5.33 d (1H, CH=C, ^2J = 0.5 Hz). PMR spectrum of (IIIb) (δ, ppm): 0.74 s (18H, t-Bu), 1.75 s (6H, MeC=C), 1.80 s (6H, MeC=C), 2.08 s (4H, CH_2). UV spectrum of (IIIb) [λ_{max}, nm (log ε)]: 256 (4.34).

3,5-Diisopropylidene-2,3,5,6-tetrahydrothiopyran-4-one (IV). Hydrogen sulfide was passed through a solution of 0.4 g of (I) in 250 ml of ethanol at 25°C for 3 h. The mixture was then evaporated and chromatographed on alumina (eluent, CCl_4) to give 0.25 g of (IV). PMR spectrum (δ, ppm): 1.84 s (6H, MeC=C), 1.98 s (6H, MeC=C), and 3.29 s (4H, SCH_2).

1-Phenyl-3,5-diisopropylidene-4-piperidone (V). A solution of 1 g of (I) and 0.5 ml of aniline in 5 ml of a 4:1 mixture of benzene and methanol was kept at 25°C for 24 h, evaporated, and chromatographed on silica (eluent, hexane) to give 0.5 g of (V). PMR spectrum (δ, ppm): 1.72 s (6H, MeC=C), 2.01 s (6H, MeC=C), 3.98 s (4H, NCH_2), 6.7-7.2 m (5H, Ph).

1,2-Diphenyl-4,6-diisopropylidene-2,3,4,5,6,7-hexahydro-1,2-diazepin-5-one (VI). To 150 ml of benzene were added simultaneously a solution of 0.1 g of (I) in 15 ml of benzene and a solution of 0.25 g of hydrazobenzene in 25 ml of a 5:1 mixture of benzene and methanol over 2 h. After 12 h, the mixture was evaporated and chromatographed on alumina (eluents, CCl_4 and chloroform). From the second eluate there was obtained 0.17 g of (VI). PMR spectrum (δ, ppm, J, Hz): 1.70 s (6H, MeC=C), 1.74 s (6H, MeC=C), 4.05 d (2H, NCH, ^2J = 15.0), 4.29 d (2H, NCH, J = 15.0), and 6.7-7.2 m (10H, Ph).

1,2,2,6,6-Pentamethyl-3-morpholinomethyl-5-methylene-4-piperidone (VIII). To 500 ml of benzene were added a solution of 0.4 g of (I) in 100 ml of benzene and a solution of 0.3 g of morpholine in 100 ml of benzene over 20 h. After 48 h, the solution was evaporated to give 0.55 g of (VIII). PMR spectrum (δ, ppm): 1.08 s (6H, Me), 1.23 s (6H, Me), 2.12 s (3H, NMe), 2.0-2.6 overlapping signals (NCH_2, CH), 3.70 t (4H, OCH_2), 4.92 s (1H, CH=C), and 5.15 s (1H, CH=C).

Preparation of Amines (IXa, b) and (XIIa). General Method. To a solution of 10 mmoles of the enone (VIII) or the dienone (XI) in 5 ml of ethanol was added all at once a solution of 12 mmoles of the appropriate amine, and after 5 h the solvent was distilled off.

1,2,2,6,6-Pentamethyl-3-morpholinomethyl-5-tert-butylaminomethyl-4-piperidone (mixture of isomers) (IXa). PMR spectrum (δ, ppm): 0.73, 0.88*, 0.98*, 1.26 s (Me), 1.04 s (t-Bu), 2.18 s (NMe), 2.2-3.2 overlapping signals (NCH_2, CH), and 3.48 br. (OCH_2).

8-Methyl-2,4-dipiperidinomethyl-8-azabicyclo[3.2.1]octan-3-one (mixture of isomers) (XIIa). PMR spectrum (δ, ppm): 1.25-1.45 overlapping signals [CH—CH, $(CH_2)_3$], 1.45-1.60 m* [$(CH_2)_3$], 1.7-1.9 m (CHCH), 2.1-2.4 (NCH_2), 2.46 s (NCH_3), 2.70 m (CHCO), and 3.64 (NCH).

8-Methyl-2,4-bis-(2-hydroxyethylthiomethyl)-8-azabicyclo[3.2.1]octan-3-one (XIIb). To a solution of 0.3 g of (XI) in 250 ml of a 9:1 mixture of benzene and ethanol was added over 3 h 0.3 g of 2-mercaptoethanol. After three days, the solvent was removed, and the residue chromatographed on silica (eluents, chloroform and a 9:1 mixture of chloroform and ethanol). From the latter eluate there was obtained 0.45 g of (XIIa). PMR spectrum (δ, ppm, J, Hz): 1.37 m (2H, CH—CH), 1.86 m (2H, CHCO), 2.20 m (2H, CH—CH), 2.53 s (3H, NMe), 2.66 t.d. (4H, SCH_2, ^3J = 5.8, J = 2.5), 2.96 m (4H, SCH_2), 3.54 m (2H, NCH), 3.64 t.m (4H, OCH_2, ^3J = 5.8).

8-Methyl-2,4-dimethylene-8-azabicyclo[3.2.1]octan-3-one (XI). To a boiling mixture of 3 g of paraformaldehyde, 0.4 g of sodium hydroxide, 80 ml of water, and 20 ml of benzene was added a solution of 1.2 g of (X) in 25 ml of benzene over 2-3 h. The cooled solution was then diluted with hexane, the organic layer separated, evaporated, and chromatographed on alumina (eluted with CCl_4) and silica (eluted with a 1:1 mixture of benzene and ether) to give 0.3 g of (XI). UV spectrum [λ_{max}, nm (log ε)]: 250 (3.81); m/z 163 (M^+). PMR spectrum (δ, ppm, J, Hz): 1.61 m (2H, CH—CH), 2.28 m (2H, CHCH), 2.28 s (3H, NCH_3), 3.82 m (2H, NCH), 5.24 d (2H, CH=C, ^2J = 2.0), and 6.08 d (2H, CH=C, ^2J = 2.0).

CONCLUSIONS

Reaction of 1,2,2,6,6-pentamethyl-3,5-dimethylene-4-piperidone with bulky nucleophiles possessing two heteroatom—proton bonds at the nucleophilic center affords six- and seven-membered saturated heterocycles.

LITERATURE CITED

1. A. M. Belostotskii and A. B. Shapiro, Khim. Geterotsikl. Soedin., No. 7, 937 (1984).
2. A. M. Belostotskii and A. B. Shapiro, Khim. Geterotsikl. Soedin., No. 9, 1248 (1986).
3. A. M. Belostotskii and A. B. Shapiro, Khim. Geterotsikl. Soedin., No. 6, 804 (1987).
4. N. S. Prostakov and L. A. Gaivoronskaya, Usp. Khim., 47, 959 (1978).
5. I. K. Korshevets and É. A. Mistryukov, Izv. Akad. Nauk SSSR, Ser. Khim., No. 7, 1540 (1987).
6. F. Johnson, Chem. Rev., 68, 375 (1968).

*Signals for one of the isomers.