PATHWAYS OF PHOTOOXIDATION OF 1,2,2,6,6-PENTAMETHYL-4-PIPERIDOL BY KETONES

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UDC 547.822.3.07:541.144.7.8:543.422'51

The photochemical oxidation of 1,2,2,6,6-pentamethyl-4-piperidol by ketones occurs exclusively at the methylamino group and, in the case of photolytically stable ketones, may lead to products of dimerization of the aminoalkyl radicals and recombination of the aminoalkyl and ketyl radicals and to a product of N-demethylation of the starting amino alcohol. When ketones that are unstable with respect to irradiation are used, photooxidation competes to a considerable extent with photodecomposition of such ketones. Spatial proximity of the aryl and α-methyl groups are observed for the products of reductive addition of the ketones on the basis of the PMR spectra.

In a study of the transformations of α-hydrogen-containing alkylamines in the well-known photoreduction of ketones chief attention was directed to their dealkylation [1]. Products of recombination of the resulting ketyl and α-aminoalkyl radicals have been isolated only in a few cases [2]. The possibility of the preparative photoaddition of ketones to the N-methyl group of tropine to give amino alcohols that are difficult to obtain by other methods and are of interest as potential pharmacologically active compounds was recently demonstrated.

In this connection we made a more detailed study of the photooxidation of 1,2,2,6,6-pentamethyl-4-piperidol (I) by ketones with various structures [4]. The structure of piperidol I contains two photoreaction centers, viz., the alkylamino and secondary hydroxy groups, and the latter also undergoes photoreactions with ketones [5]. Although it is known that alcohols are inferior to amines as photoreducing agents [2], one cannot with certainty predict the degree of participation of each of the potential reductive centers of cycloaminoalkanol I. Moreover, photoreduction could compete with decomposition of the ketones, which, depending on their structure, have different resistances to irradiation [6].

The reaction of amino alcohol I with ketones of both aromatic and nonaromatic character, viz., benzophenone (IIa), xanthone (IIb), acetophenone (IIc), 1,2-diphenylethanone (IId), 1,3-

TABLE 1. Products of Photooxidation of 1,2,2,6,6-Pentamethyl-4-piperidol by Ketones IIa-e, g

Ketone II	Irradiation time, h	Yield,* %		
		III	IV	V
a	6	32	24	28
b	28	22	9	44
c	7	24	4	41
d	7	27	15	30
e	38	8 (17)	23 (46)	9 (18)
g	7	21	51	2

*The numbers without parentheses designate the yields based on the amount of amine I subjected to the reaction, while the numbers in parentheses designate the yields based on the converted amine.

Scientific-Research Institute of Pharmacology of the Academy of Medical Sciences of the USSR, Moscow 125315. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1657-1661, December, 1982. Original article submitted March 25, 1982.

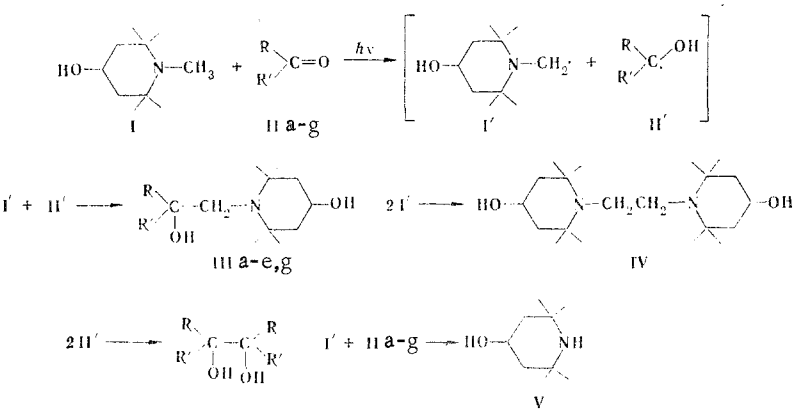
 0009-3122/82/1812-1280$07.50

TABLE 2. Products of the Reductive Addition of IIIa-e, g

III	-2,2,6,6-tetramethyl-4-piperidol	mp, °C	Chemical shift, ppm: α-methyl groups	Chemical shift, ppm: N—CH₂	Chemical shift, ppm: 4-H	M⁺	Found, %: C	Found, %: H	Found, %: N	Empirical formula	Calc., %: C	Calc., %: H	Calc., %: N
a	1-(2-Hydroxy-2,2-diphenylethyl)-	228—229	0,58; 0,58; 1,00; 1,00	3,61	3,99	353	78,6	8,8	4,0	$C_{23}H_{31}NO_2$	78,2	8,8	4,2
b	1-(9-Hydroxy-9-xanthenyl) methyl-	196—197	0,69; 0,69 0,78; 0,78	2,64	3,79	367	75,1	8,0	4,0	$C_{23}H_{29}NO_3$	75,3	7,9	3,8
c	1-(2-Hydroxy-2-phenylpropyl)	185—186	0,32; 0,83; 1,03; 1,32	2,79	4,10	291	74,1	9,9	4,9	$C_{18}H_{29}NO_2$	74,3	10,0	4,8
d	1-(2-Hydroxy-2,3-diphenylpropyl)	189—191	0,34; 0,97; 1,20; 1,35	3,19	3,98	367	78,4	9,0	3,8	$C_{24}H_{33}NO_2$	78,5	9,0	3,8
e	1-(2-Hydroxy-2,4-diphenylbutyl)-	177—179	0,39; 0,94; 1,12; 1,25	3,15	4,01	381	78,8	9,1	3,9	$C_{25}H_{35}NO_2$	78,8	9,2	3,7
g	1-(2-Hydroxy-2-methylpropyl)-	86—88	1,13; 1,13; 1,15; 1,15	2,57	3,98	229	73,5	12,0	6,0	$C_{13}H_{27}NO_2$	73,8	11,8	6,1

diphenyl-1-propanone (IIe), benzoin (IIf), acetone (IIg), 2-butanone (IIh), 1-phenyl-2-propanone (IIi), 1-acetyladamantane (IIj), 2-acetylfuran (IIk), and 2-acetylthiophene (IIℓ), was examined. The photolysis was carried out in benzene at an amine—ketone ratio of 1:2 (except for the reaction with ketones IIg, h) and at an amine concentration of 0.1 mole/liter until one of the starting substances vanished or equilibrium was established [according to monitoring by gas—liquid chromatography (GLC)].

It was shown that the photooxidation of piperidol I by ketones proceeds at the reaction center bonded to the amino group. An analysis of the mixture of amines formed in the reaction by GLC did not demonstrate the presence of compounds other than those subsequently isolated products of reaction at the alkylamino group (the amines were isolated in the form of hydrochlorides and were then converted to the bases). The formation of all three possible amino-containing compounds, viz., products of the reductive addition of an α-aminoalkyl radical to the ketyl radical (IIIa-e, g), a product of dimerization of the aminoalkyl radicals (IV), and a demethylation product — 2,2,6,6-tetramethyl-4-piperidol (V) — is characteristic for photolysis-resistant ketones IIa-e, g (Table 1). The simultaneously formed pinacols were not



II, III a R=R′=Ph; b R+R′=*o,o*-C_6H_4—O—C_6H_4; c R=Ph, R′=Me; d R=Ph, R′=CH_2Ph; e R=Ph, R′=CH_2CH_2Ph; f R=Ph, R′=CH/OH/Ph; g R=R′=Me

isolated. The structure of the 2,2-disubstituted 1-(2-hydroxyethyl)-2,2,6,6-tetramethyl-4-piperidols IIIa-e, g was confirmed by data from the PMR and mass spectra and the results of elementary analysis (Table 2). It was established that when the concentration of ketones IIa, c was increased by a factor of two as compared with the previously used concentrations [4], although it did decrease the yields of dimer IV (by 10 and 39%, respectively), the yields of cross products IIIa, c increased slightly (by 1 and 14%) as compared with increases in the yields of dialkylation product V (by 38 and 37%).

Demethylated piperidol V and dimer IV in 61 and 9% yields, respectively, together with products of polymeric character, were isolated when amine I was irradiated with hydroxy ketone IIf for 27 h. The reaction with heterocyclic ketones IIk, ℓ proceeds with low degrees of conversion. According to GLC data, virtually no consumption of the reagents occurs after

the formation of dealkylation product V in 10-15% yields. The inertness of 2-heteryl methyl ketones IIk, l in this reaction is in agreement with the previously described [7, 8] low reactivities of α-benzoylated heterocycles in their photoreduction with isopropyl alcohol.

In the reaction with photolabile ketones IIi, j analysis by GLC establishes rapid disappearance of the ketone (even when an excess amount is used), whereas starting amine I is not consumed completely; this indicates photodecomposition of the ketones. This conclusion was confirmed by the formation of carbon monoxide in the photolysis of a mixture of amine I and ketone IIi and its absence in a control experiment with a mixture of irradiation-resistant ketone IIa with amine I (the carbon monoxide was trapped with a solution of palladium chloride by the method in [9]). The result of the reaction with the participation of ketones IIi, j was the formation of complex mixtures of amino-containing compounds, the chromatographic mass spectrometric analysis of which demonstrated the presence of dealkylation product V(M^+ 157); peaks of molecular ions of products of cross recombination of the III type or of dimer IV were not observed. Piperidol V and diamino diol IV in 38 and 17% yields, respectively, together with a difficult-to-separate mixture of amino-containing compounds, were obtained in the reaction with the more stable aliphatic ketone IIh.

Thus, depending on the photolytic stability of the ketones, the photooxidation of piperidol I competes with the photodecomposition of the ketones, and the formation of reductive addition products of the III type should be expected when irradiation-resistant ketones of the aromatic and aliphatic-aromatic series or stable aliphatic ketone IIg are used.

The inertness of the secondary hydroxy group of 4-piperidols in the photooxidation by ketones was confirmed by the absence of a reaction between reactive ketone IIa and amine V, which does not have α-hydrogen atoms. The starting compounds were recovered quantitatively after photolysis in benzene for 17 h.

A comparison of the position of the PMR signals of the gem-dimethyl groups of the piperidine ring in starting piperidol I (s, 1.09 ppm, $2CH_3$; s, 1.18 ppm, $2CH_3$) with the signals of the same groups in the spectra of products IIIa-e indicates the spatial proximity of these substituents with respect to the exocyclic aryl rings. The 0.4-0.5 ppm shift of the signals of the two methyl groups to strong field for IIIa, b and the 0.6-0.75 ppm strong-field shift of one of the methyl groups for IIIc-e evidently arise because of the shielding effect of the magnetically anisotropic field of the phenyl groups (Table 2). Changes in the position of the chemical shift of the signals of the gem-dimethyl groups of the piperidine ring do not occur in the case of aliphatic analog IIIg. A singlet signal of each α-methyl group as a consequence of the diastereotropic character of both the axial and equatorial substituents appears in the spectra of IIIc-e, which have an asymmetric center. The diastereotropic character of the protons of the N–CH_2 group of these compounds did not show up in the spectra, and a singlet signal over the range from 2.57 to 3.61 ppm is observed for all products IIIa-e, g; however, the methylene protons are nonequivalent (s, 3.70 ppm; s, 3.73 ppm) in the spectrum of the hydrochloride of IIIc (in D_2O). A complex multiplet of a methylidyne proton in the 4 position of the piperidine ring centered at 3.79 to 4.10 ppm is also characteristic for the PMR spectra of products IIIa-e, g.

EXPERIMENTAL

The photolysis was carried out in a quartz flask with external irradiation by means of two PRK-2M lamps (with an overall power of 750 W) as the solvent was allowed to reflux and argon was bubbled into the mixture. The distance from each irradiation source to the wall of the flask was 15 cm. For gas–liquid chromatography (GLC) was used a Tsvet-152 chromatograph with a 1 m by 3 mm column filled with 5% SE-30 on Chromaton N-AW; the carrier gas was nitrogen, the temperature was programmed from 75 to 280°C, and the program rate was 12°C/min. Chromatographic mass spectrometry was carried out with a Varian MAT-122 spectrometer under the same GLC conditions (except that the carrier gas was helium); the ionizing voltages were 40 and 70 eV, and the ionization-chamber temperature ranged from 100 to 250°C. The PMR spectra of solutions in $CDCl_3$ were recorded with a Varian T-60 spectrometer (60 MHz) with hexamethyldisiloxane as the internal standard. Separation was accomplished with columns filled with silica gel (50-100 μ); column A was 3 by 45 cm, while column B was 1.5 by 12 cm. The UV absorption of the eluates was determined at 260 nm by means of an RÉPPS-M flow recorder (Central Design Office of the Academy of Medical Sciences of the USSR). Thin layer chromatography (TLC) was carried out on Silufol plates in a chloroform–alcohol system (3:1). Amine V was sublimed at 100-103°C. The melting points were determined with a Boetius heating stage.

Photolysis of Amine I and Ketones IIa, c-f (typical method). A solution of 1.5 g (8.8 mmole) of the amine and 17.6 mmole of the ketone in 90 ml of benzene was irradiated with GLC monitoring every 5-6 h (the reaction mixture was transferred to another flask if a polymeric layer formed on the bottom). The reaction mixture was extracted with 1 N HCl solution (two 50-ml portions), the aqueous phase was washed with benzene, and the organic phase was washed with water. The combined aqueous extracts were made alkaline to pH 10-11 with NaOH solution, and the resulting precipitate was removed by filtration, washed with water, dried over KOH, and dissolved in 100-150 ml of chloroform. The solution was evaporated with 10 g of silica gel and applied to column A, and elution was carried out successively with 0.8-1.5 liters of chloroform and 0.8 liter of chloroform–methanol (4:1) with collection of 20-ml fractions. Compounds IIIa, c-e were detected from the UV absorption of the chloroform eluate (polymeric products were isolated in the case of ketone IIf), while dimer IV was detected by TLC in fractions of the mixed eluate. Compounds IIIc, e were rechromatographed with column B (the compounds were applied in chloroform and were eluted with chloroform saturated with NH_3). The aqueous alkaline solution was saturated with potassium carbonate and extracted with chloroform (three 150-ml portions). The organic phase was dried with $CaCl_2$, the solvent was evaporated, and the residue was sublimed to give piperidol V. In the case of the reaction of amine I with ketone IIe, from the aqueous alcohol solution we similarly isolated a mixture of starting amine I and secondary amine V, the yields of which were determined by GLC. 4,4'-Dihydroxy-2,2,2',2',6,6,6',6'-octamethyl-1,1'-ethylenebispiperidine (IV) has mp 265-266°C. PMR spectrum of the dihydrochloride of IV (in D_2O): 1.42 (s, $4CH_3$, 12H), 1.50 (s, $4CH_3$, 12H), 1.70-2.42 ($4CH_2$, 8H), 3.56 (s, $2N{-}CH_2$, 4H), and 4.18 ppm (m, 2H, 2H).

Photolysis of Amine I and Ketone IIb. A solution of 1.5 g of amine I and 3.45 g (17.6 mmole) of ketone IIb in 90 ml of benzene was irradiated with removal of the resulting precipitate every 5-6 h. Chromatography of the precipitate with column A by the typical method gave IIIb and IV, and the latter was purified by the typical method with column B. The benzene filtrate of the reaction mixture was evaporated to dryness, 30 ml of 1 N HCl solution was added to the residue, and the mixture was extracted with chloroform (three 30-ml portions). The aqueous extract was made alkaline to pH 10-11 with NaOH solution and filtered, and the filtrate was saturated with potassium carbonate. Amine V was extracted with chloroform (three 100-ml portions) and purified by sublimation.

Photolysis of Amine I and Ketone IIg. A solution of 1.5 g of amine I and 19.8 g (0.34 mole, 25 ml) of ketone IIg in 65 ml of benzene was irradiated, after which it was evaporated to dryness, and the residue was refluxed for 30 min in 0.25 N HCl solution. The resulting solution was cooled to 20°C and extracted with chloroform (two 50-ml portions). The aqueous phase was made alkaline to pH 10-11, and the precipitate was removed by filtration, washed with water, dried over KOH, and purified by the typical method with column B to give dimer IV. The aqueous alkaline solution was saturated with potassium carbonate and extracted with chloroform (three 100-ml portions). The extract was dried with $CaCl_2$ and concentrated, and the concentrate was chromatographed with column B [successive elution with chloroform–alcohol (7:1) and chloroform saturated with NH_3; 2.5-ml fractions were collected]. The fractions were subjected to TLC; the fractions corresponding to the upper spot in TLC were evaporated, the residues were dissolved in water at pH 5-6, and the solutions were applied to 15 ml of Dowex-50W × 4 resin (the H^+ form). The substance was eluted with 1.5 N HCl solution; the hydrochloride of IIIg was obtained after evaporation and drying. The hydrochloride was converted to the base by refluxing with piperidine for 1 min. Amine V was obtained from the fractions corresponding to the lower spot in TLC after two sublimations.

Photolysis of Amine I and Ketone IIh. Dimer IV (17%) was obtained via the preceding method [from 20 g (0.33 mole, 25 ml) of ketone IIh; the irradiation time was 18 h]. A mixture of four compounds was detected after separation with column B [successive elution with chloroform, chloroform–alcohol (7:1), and chloroform saturated with NH_3] in the fractions of the chloroform eluate from GLC; V (38%) was isolated from the subsequent fractions.

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BROMINATION OF 1-ALKYL-2-PYRIDONES

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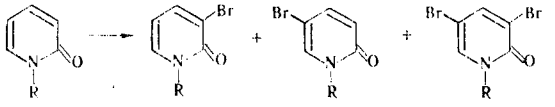
UDC 547.824:542.944.2:543.422.25

The corresponding monobromides were obtained in the bromination of 1-alkyl-2-pyridones with bonded bromine (with N-bromosuccinimide and dioxane dibromide). The conditions under which the yields of the mixtures of isomers were 60-80%, and almost no dibromides were obtained, were found. It was established that the ratios of the 3- and 5-bromo isomers depend on the character of the brominating agent.

It is known from the literature data that the bromination of 2-pyridones generally leads to 3,5-dibromo-substituted compounds [1, 2]. Up until now, the monobromination of 1-alkyl-2-pyridones has not been accomplished.* In the present research we studied the bromination of 1-alkyl-2-pyridones [1-methyl-, 1-ethyl-, and 1-butyl-2-pyridone (I-III)] by means of various brominating reagents, viz., bromine, dioxane dibromide, and N-bromosuccinimide, in order to investigate the orientation and also to obtain monobromides with the goal of subjecting them to further functionalization. Considerable amounts of dibromopyridones are formed along with monobromides in the reaction of bromine with alkylpyridones even at negative temperatures (see Table 1). Only bromination with bonded bromine (using dioxane dibromide and N-bromosuccinimide) completely excludes the formation of dibromides. We have shown that the bromination of pyridones I-III with dioxane dibromide and N-bromosuccinimide under various temperature conditions gives mixtures of 3-bromo-1-alkylpyridones (IVa-c) and 5-bromo-1-alkylpyridones (Va-c) (in 60-80% overall yields), which were isolated in individual form by means of column chromatography.



I-III IVa-c Va-c VIa-b

I, IV-VIa R = CH_3; II, IV-VIb R = C_2H_5; III, IV-Vc R = C_4H_9

It is apparent from the data in Table 1 that approximately equal amounts of 3- and 5-monobromides (IVa and Va) are formed when dioxane dibromide is used. Bromination with a more selective reagent — N-bromosuccinimide — gives primarily 5-bromo isomers V and can be used for the preparative synthesis of these compounds. A change in the temperature conditions had almost no effect on the overall yields of the bromination products and the ratios of 3- and 5-bromo isomers IV and V, which were determined by means of gas—liquid chromatography (GLC). The assignment of the signals of the protons of the pyridone ring in the PMR spectra of the bromination products was made on the basis of their multiplicities and also on the basis of the spin—spin coupling constants (SSCC), which, in agreement with the literature data [4], are larger for J_{34} than for J_{45} (see Table 2).

The results show that despite the calculated data [5], the 5 position of the pyridone ring is more reactive in bromination than the 3 position.

*The 3- and 5-bromo-substituted pyridones described in the literature were obtained from the corresponding bromoaminopyridines [3].

M. V. Lomonosov Moscow State University, Moscow 117234. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1662-1664, December, 1982. Original article submitted March 24, 1982.

 0009-3122/82/1812-1284$07.50