Found: C 59.5; H 5.4; N 10.7%; M 262 by mass spectrometry. $C_{13}H_{14}N_2O_4$. Calculated: C 59.5; H 5.4; N 10.7%; M 262.26.

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SYNTHESIS AND STEREOCHEMISTRY OF N-SUBSTITUTED 3,5-DIBENZOYL-4-PHENYLPIPERIDINES*

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UDC 547.828.829.07:541.63

The addition of methyl-, benyl-, cyclohexyl, and 2-hydroxyethylamines and hydroxylamine to 2,4-dibenzoyl-3-phenyl-1,4-pentadiene in dimethylformamide leads to the formation of stereoisomers of the corresponding N-substituted 3,5-dibenzoyl-4-phenylpiperidines in almost quantitative yields. The configurations of the stereoisomers obtained were determined by PMR spectroscopy, and their interconversions under the influence of alkali were studied.

In a preliminary communication [2] we described the formation of the α and β forms of N-substituted 3,5-dibenzoyl-4-phenylpiperidines (II, III) by the reaction of, respectively, methyl- and benzylamine with 2,4-dibenzoyl-3-phenyl-1,4-pentadiene (I). In the present paper we present data on the addition of primary amines and hydroxylamine to diketone I and on the stereochemistry and interconversions of the resulting stereoisomeric piperidines II-VI.

*Communication 34 from the series "Reactions of 1,5-Diketones." See [1] for communication 33.

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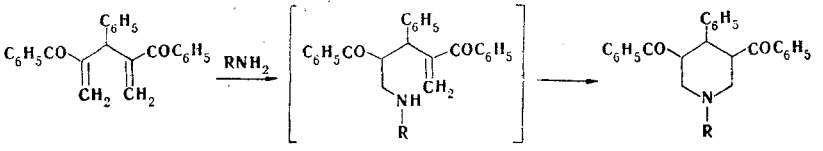
TABLE 1. N-Substituted 3,5-Dibenzoyl-4-phenylpiperidines II-VII

Compound	mp, °C (dec.)	$R_f \times 100$	M^+, m/e	IR spectrum, ν, cm^{-1}		Found, %			Empirical formula	Calculated %			Yield*, %
				C=O	OH	C	H	N		C	H	N	
IIα	209—210	50	383	1685	—	81,5	6,8	3,8	$C_{26}H_{25}NO_2$	81,4	6,6	3,7	96
IIβ	179—181	8	—	1685	—	81,4	6,7	3,8					
IIIα	145—146	88		1680	—	83,4	6,4	3,0	$C_{32}H_{29}NO_2$	83,6	6,4	3,0	98
IIIβ	206—208	60		1680	—	83,6	6,2	3,1					
IVα	173—174	80		1690	—	82,2	7,9	3,4	$C_{31}H_{33}NO_2$	82,4	7,4	3,1	99
IVβ		25			—								
Vα	159—160	38		1680	3620, 3450	78,2	6,6	3,6	$C_{27}H_{27}NO_3$	78,4	6,6	3,4	92
Vβ		10											
VIα	188—190	63	385	1685	3300, 3580	77,8	6,1	3,6					
VIβ	174—176	22	385	1690	3300, 3590	77,8	6,5	3,7	$C_{25}H_{23}NO_3$	77,9	6,0	3,6	96
VIγ	173—174	48		1680	3300, 3580	78,3	6,3	3,6					
VIIα	146—147	76	427	1690, 1760	—	76,1	6,0	3,6					
VIIβ	171	58		1690, 1760	—	75,5	5,9	3,5	$C_{27}H_{25}NO_4$	75.9	5,9	3,3	
VIIγ	146	71		1685, 1760	—	76,1	6,8	3,7					

*The yields of the mixtures of stereoisomers are presented.



I II-VI

II R=CH_3; III R=$CH_2C_6H_5$; IV R=cyclo-C_6H_{11}; V R=CH_2CH_2OH; VI R=OH

The reaction takes place in dimethylformamide (DMFA) at room temperature and gives the products in almost quantitative yields.

The structures of II-VI (Table 1) follow from a comparison of their IR spectra with the spectrum of diketone I [3], which has absorption bands at 1660 (C=O) and 1630 cm^{-1} (C=CH_2). The IR spectra of piperidines II-VI do not contain the absorption of a C=CH_2 group, but a C=O band is found at 1680-1690 cm^{-1}.

Each II-V consists of a mixture of two α and β stereoisomers, while VI consists of a mixture of three isomers — α, β, and γ. The isomer ratios IIα : IIβ = 3 : 1 and VIα : VIβ : VIγ = 11 : 8 : 1 were found by means of column chromatography on silica gel. The α isomers in the remaining cases are obtained in high yields. They have large R_f values, similar PMR spectra (Table 2), and, except for III α, are characterized by higher melting points and lower solubilities than the corresponding β isomers.

The action of catalytic amounts of NaOH on alcohol solutions of IIβ-Vβ leads to their isomerization to the corresponding IIα-Vα. Under these conditions, isomer VIβ is converted to VIα through the intermediate formation of VIα. The isomerization evidently proceeds through enolization of the carbonyl groups and probably may be catalyzed by the starting amines and by the resulting piperidine itself; the latter may serve as an explanation for the unusual difficulty in the isolation of samples of the β isomers that do not contain admixed α isomers. An increase in the reaction time for diketone I with, for example, methylamine to 3 days leads to virtually only piperidine IIα; only traces of the IIβ isomer were detected (by the thin-layer chromatography (TLC)).

In the case of the isomers of VI, their N-acetoxy derivatives (VII), which give more resolved PMR spectra, were obtained by the method in [4]. Calculation by the method in [5] of the PMR spectrum of isomer VIIγ, which is a combination of two equivalent ABK spin systems and a K_2M system (of the A_2B type), leads, with good agreement between the calculated and observed intensities of the transitions, to spin—spin coupling constants (SSCC) and chemical shifts (presented in Table 2 in parenthesis), the deviations of which from the first-order parameters are within the limits of error in recording the spectrum. For the stereochemical interpretation of the spectra one may therefore limit oneself to an examination of the first-

TABLE 2. PMR Spectra of II-VII

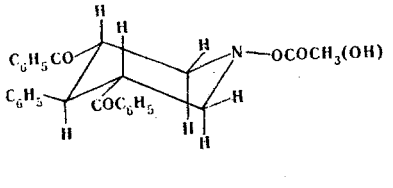
Compound	δ, ppm (± 0.01 ppm)								J, Hz (± 0.3 Hz)							
	N—R	2a-H	6a-H	6e-H	2e-H	4a-H	5e-H	3a-H	C_6H_5	2a2e	6a6e	2a3a	2e3a	3a4a	4a5e	5e6a	5e6e
IIα	2,20 s (3H)	2,10	2,59	3,13	3,26	3,59	4,17	5,44	6,88—8,16	−11,4	−12,0	10,9	3,8	10,6	4,7	4,4	2,6
IIIα	3,46q (2H)*	2,30	2,62	3,18	3,28	3,66	4,10	5,40	6,68—8,09	−11,2	−11,9	10,5	3,8	10,3	4,5	3,7	3,2
IVα	1,01—2,28 (11H)	2,51	2,84	3,26	3,26	3,60	4,10	5,29	7,00—8,15	−11,2	−11,7	10,3	3,8	10,6	4.4	3,8	3,2
Vα	3,4 t (2H), 2,5 t (2H)	2,39	2,79	3,19	3,19	3,66	4,15	5,31	6,76—8,09	−11,4	−12,0	10,3	3,8	10,9	4,7	4,1	2,6
VIIα	1,89 s (3H)	3,10	3,40	3,70	3,70	3,88	4,31	5,29	6,99—8,11	−11,2	−11,7	10,0	4,1	9,4	4,7	4,7	4,4
	N—R	2a-H, 6a-H(2H)		2e-H, 6e-H(2H)		4H	3-H, 5-H(2H)		C_6H_5	2a2e, 6a6e		2e3, 56e		2a3, 56a		34, 45	
IIβ	2,59s (3H)	3,02d (4H)				3,88	4,24		6,53—7,67			15,8 ($J_{2a3}+J_{2e3}$)				5,9	
IIIβ	3,83 s (2H)	3,08 d (4H)				3,90	4,22		6,53—7,66			15,8	„			5,6	
VIIβ	2,14 s (3H)	3,62 (4H)				3,86	4,47		6,52—7,66			15,8	„			5,9	
VIγ	—	3,14		3,57		3,83	4,75		6,88—7,82	−12,6		3,5		11,4		10,9	
VIIγ	2,07 s (3H)	3,04 (3,05)		3,69 (3,69)		3,77 (3,78)	4,49 (4,49)		6,92—7,82	−11,1 (−11,12)		3,5 (3,49)		11,5 (11,53)		11,4 (11,49)	

*Center of an AB quartet with $\Delta\delta_{AB}$ 0.28 ppm and $|J_{AB}|$ = 12.5 Hz.

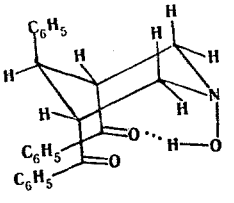
order parameters, especially since the corresponding $J/\nu_0\delta$ values, which determine the degree of deviation of the first-order parameters from the true parameters, are even smaller in the remaining cases.

The signal of the two enantiotopic 3-H and 5-H protons in the PMR spectrum of VIIγ lies at 4.49 ppm and has the form of a sextet as a consequence of partial summation of 16 principal transitions with SSCC of 11.4, 11.5, and 3.5 Hz. This is in agreement with an axial orientation of both 3-H and 5-H and 4-H (δ 3.77 ppm, a triplet because of merging of the two middle lines of the quartet, J = 11.4 Hz). The protons of the two methylene groups form an axial (2a-H, 6a-H, δ 3.04 ppm, SSCC 11.1 and 11.5 Hz) and equatorial (2e-H, 6e-H, δ 3.69 ppm, SSCC 11.1 and 3.5 Hz) enantiotopic pairs. Compound VIIγ (VIγ) is consequently N-acetoxy(hydroxy)-3t,5t-dibenzoyl-4r-phenylpiperidine, i.e., the meso form.

The relatively small absolute value of the geminal SSCC of the VIIγ isomer (11.1 Hz) is in agreement with the data in [6] on the positive contributions to the geminal SSCC of the axially oriented free pair of electrons of the nitrogen atom in the α position and of the β substituent lying within the dihedral angle of the geminal protons and the C_2-C_3 bond. The higher absolute value of the geminal SSCC in the VIγ isomer (12.6 Hz) is probably due to the increased contribution of the conformation with an axial orientation of the substituents that is stabilized by the formation of an intramolecular hydrogen bond. The latter is possibly also the reason for the formation of this isomer.



VII γ (VI γ)



VI γ

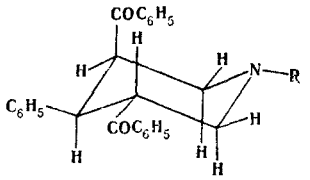
The signals of the 4-H protons at 3.6-3.9 ppm in the PMR spectra of IIα-VIIα are quartets with SSCC of ∿ 10.5 and 4.5 Hz, which is in agreement with an axial orientation of 3-H and 4-H and an equatorial orientation of 5-H. The 3a-H signals at 5.2-5.4 ppm appear as sextets of the same form as in the spectrum of isomer VIIγ with two SSCC of ∿ 10.5 Hz and one SSCC of ∿ 4 Hz. The signals of the 5e-H protons lie at 4.1-4.3 ppm in the form of poorly resolved quartets with three SSCC of ∿ 4 Hz. The IIα-VIIα isomers are consequently 3t,5c-dibenzoyl-4r-phenylpiperidines, i.e., the threo forms.

The different orientation of the benzoyl groups is responsible for the observed differences in the positions of the signals of the axial and equatorial protons of the two methylene groups and the 3a-H and 5e-H signals (Table 2), since, as demonstrated for a series of

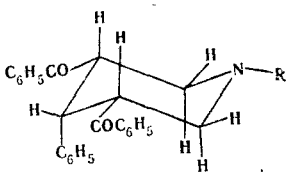
cyclohexane derivatives [7], the 1e-substituent shifts the chemical shifts of the 2α-H and 2e-H protons to the strong-field side but has almost no effect on the 3-H protons. The 1a-substituent [7] shifts the 2e-H chemical shifts to the strong-field side but changes the 2α-H and, to an even greater extent, 3α-H chemical shifts to the weak-field side.

It should be noted that the diastereotopic N-benzyl protons in the PMR spectrum of isomer IIIα appear as an AB quartet, in agreement with the data in [8].

Since a molecule with two identical asymmetric (C_3 and C_5) centers and one pseudoasymmetric (C_4) center can exist in the form of one racemate (the threo form) and two meso forms, the β isomers are evidently the second meso form of the compounds, i.e., 3c,5c-dibenzoyl-4r-phenylpiperidines.



IIα–VIIα



IIβ–VIIβ

The PMR spectra of the IIβ, IIIβ, VIβ, and VIIβ isomers correspond to symmetrical compounds and are degenerate ABX systems. The signals of four methylene protons (the AB part) in the spectrum of piperidines IIβ and IIIβ appear in the form of a doublet at 3.02 and 3.08 ppm, respectively, with an apparent SSCC of 7.9 Hz, which is equal to $^1/_2(J_{AX} + J_{BX})$ when $\Delta\delta_{AB} = 0$, i.e., an AA'X system obtains here. The X parts of the systems (3-H,5-H), which also couple with the 4-H protons with SSCC of 5.9 Hz, appear as a consequence of partial summation of the transitions in the form of quartets at 4.24 and 4.22 ppm for IIβ and IIIβ, respectively. The spectrum of acetoxypiperidine VIIβ is a system that occupies an intermediate position between the ABX and AA'X types, where the AB part is a quintet of the irregular form with its center at 3.62 ppm and $(J_{AX}+J_{BX})$ = 15.8 Hz (determined from the X part), whereas the X part (3-H, 5-H) is a quintet due to additional coupling with 4-H with an SSCC of 5.9 Hz and partial summation of the transitions. According to [7], such close agreement between the chemical shifts of the equatorial and axial methylene protons can be explained by the considerable shift of the latter to weak field due to predominance of the conformation with a 4a orientation of the phenyl group.

EXPERIMENTAL

Monitoring of the course of the reactions and evaluation of the individuality of the compounds were accomplished by means of TLC on Silufol in a benzene–ethyl acetate system (1 : 1) with development of the spots by means of iodine vapors. The melting points of the compounds were determined with a Boëtius apparatus. The IR spectra of solutions of the compounds in $CHCl_3$ and CH_2Cl_2 were recorded with a UR-20 spectrometer. The PMR spectra of solutions of the compounds in $CDCl_3$ were recorded with a Bruker HX-90E spectrometer (90 MHz) at room temperature with tetramethylsilane as the internal standard. The mass spectra were recorded with an MKh-1303 spectrometer at 30 eV.

Addition of Amines to Diketone I. A 0.04-mole sample of the amine* was added to a solution of 7.05 g (0.02 mole) of diketone I [3] in 150 ml of DMF, and the mixture was allowed to stand overnight. The solution was diluted with water, and the crystalline reaction product was removed by filtration, washed with water, and dried (see Table 1). The individual compounds were isolated by fractional crystallization from methanol or by means of column chromatography on silica gel. Partial separation of the stereoisomers was also achieved by their fractional precipitation from the reaction mixture by the addition of water.

Action of Sodium Hydroxide on Stereoisomeric Piperidines II-V. A 0.5-ml sample of a saturated solution of NaOH in CH_3OH was added to a solution of 0.3 g of II in 30 ml of CH_3OH at room temperature. After a few minutes, isomer IIα appeared in the solution, and isomer

*In the case of methylamine a 25% aqueous solution was used. In the case of the addition of hydroxylamine in aqueous solution of its hydrochloride containing an equivalent of NaOH was used.

IIβ vanished after ∿ 2 h (as monitored by TLC). The isolated IIα was identical to a sample of the compound obtained as described above according to its melting point and IR spectrum.

Similar transformations were observed for isomers IIIβ-Vβ. Analytical samples of the β isomers were not isolated in the case of IV and V, while isomerization was observed for mixtures of the α and β isomers, from which the β isomers vanished.

Action of Sodium Hydroxide on Stereoisomeric N-Hydroxypiperidines VI. Under the conditions presented above, VIα was converted to isomer VIγ in the course of a few hours. Isomer VIβ was also converted to N-hydroxypiperidine VIγ under the influence of NaOH, and monitoring by TLC showed that isomer VIα, which was subsequently converted to isomer VIγ in a few hours, was formed in the first rapid step (∿ 10 min). When NaOH was added, acetoxy derivatives VII underwent decomposition to N-hydroxy derivatives VI, which were isomerized as described above.

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HYDROGENATED AZOLO- AND AZINOPYRIDINES BASED ON 1,5-DIKETONES

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Compounds that contain a hydrogenated azolopyridine structure are formed in the reaction of various types of 1,5-diketones with ethanolamine, o-aminophenol, o-phenylenediamine, and aroylhydrazines; compounds that include a hydrogenated azinopyridine structure were obtained by the reaction of diketones with 3-aminopropanol and anthranilic acid. The hydrocyanation and oxidation of the compounds obtained were studied.

The reactions of alkylidene(arylidene) dicyclohexanones with ethanolamine [1] and o-aminophenol and o-phenylenediamine [2] have been previously studied. To establish the general character of the reactions of 1,5-diketones with primary amines that contain a nucleophilic center in the β or α position relative to the amino group we investigated the action of aliphatic-aromatic (Ia), alicyclic (Ib), "semicyclic" (Ic, d), and other (Ie-j) 1,5-diketones on ethanolamine, 3-aminopropanol, o-aminophenol, o-phenylenediamine, anthranilic acid, and aroylhydrazines. The typical pathway is dual cyclization: when the nucleophilic center is in the β position, derivatives of hydrogenated azolopyridines (II, IV, V, and VII-IX) are formed, whereas derivatives of hydrogenated azinopyridines (III, VI) are formed when the nucleophilic center is in the γ position.

When unsymmetrical diketones Ic-i are used, an azole or azine ring is formed in the direction of the alicyclic fragment of the diketone. However, "dihydropyridine" derivative XIIIh is formed instead of a derivative of the benzoxazinopyridine type (VI) in the reaction of diketone Ih with anthranilic acid, and this indicates the lower tendency for cyclization of the cyclopentanone fragment.

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