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HETEROCYCLIZATION OF OXIMES OF 3,5-DIMETHYL(1,3,5-TRIMETHYL)-2,6-DIPHENYLPIPERID-4-ONES AND N-BENZYLPYRROLID-3-ONES WITH ACETYLENE IN A SUPERBASIC MEDIUM

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It has been established that on heterocyclization of 3,5-dimethyl-2,6-diphenylpiperid-4-one oxime with acetylene in a superbasic medium migration of the 3a-CH_3 group to the anionic nitrogen atom occurs, leading to the formation of 5,7-dimethyl-4,6-diphenyl-4,5,6,7-tetrahydropyrrolo[3,2-c]pyridine. The formation of the N-anion causes aromatization of the tetrahydropyridine ring. Tetrahydropyrrolo-[1,2-c]pyrimidines are formed in the Trofimov reaction as a result of decomposition of the intermediate 3H-pyrrole in a retro-Mannich reaction.

Keywords: oxime, pyrrole, pyrrolidine, tetrahydropyrrolo[3,2-*c*]pyridine, heterocyclization.

The heterocyclization of oximes of piperid-4-ones with acetylene in a superbasic medium (the Trofimov reaction) has enabled preparative methods to be developed for obtaining 4,5,7-trimethyl-4,5,6,7-tetrahydropyrrolo[3,2-c]pyridine [1] and 2,4,5-trimethyl-1,2,3,4-tetrahydropyrrolo[1,2-*c*]pyrimidine [2] and a systematic study to begin on the reactivity of these heterocyclic structures containing two pharmacophoric rings [3-6]. Meanwhile many aspects of the Trofimov reaction in a series of nitrogen-containing cyclic ketones remain unclarified. In particular the effect of the ring size of the heterocyclic ketone and the mutual disposition of the nitrogen atom and the oxime grouping on the course of the Trofimov reaction have not been studied. The chemical mechanism of the formation of tetrahydropyrrolo[1,2-*c*]pyrimidines under the conditions of the Trofimov reaction remains unclear.

On heterocyclization of 3,5-dimethyl-2,6-diphenylpiperid-4-one (**1**) in the presence of KOH the expected main product of heterocyclization, 4,5-dimethyl-1,3-diphenyl-1,2,3,4-tetrahydropyrrolo[1,2-*c*]-pyrimidine (**2**), was not isolated [7]. Depending on the reaction conditions either 4,5-dimethyl-1,3-diphenylpyrrolo[1,2-*c*]pyrimidine (**3**), the product of aromatization of compound **2** (atmospheric pressure, 90-95°C) was obtained, or 2-ethynyl-7a-hydroxy-3a,7-dimethyl-4,6-diphenylperhydropyrrolo[3,2-*c*]pyridine (**4**) was formed as a mixture of four isomers according to the mutual disposition of the 3a-CH_3 and 2-ethynyl groups and the junction of the piperidine and pyrrolidine rings (autoclave, 80-90°C).

Results are correlated in the present communication on the study of the heterocyclization of oxime **1** with acetylene at 70°C, of 1,3,5-trimethyl-2,6-diphenylpiperid-4-one oxime (**5**) and of the oximes of 1-benzyl- (**6**), 1-benzyl-2-methyl- (**7**), and 1-benzyl-4-methylpyrrolid-3-ones (**8**). The pyrrolid-3-ones required for carrying out this work were synthesized by the intramolecular condensation of esters of the corresponding 3-benzylaminohexane-1,6-dicarboxylic acids under conditions of the Dieckmann reaction [8].

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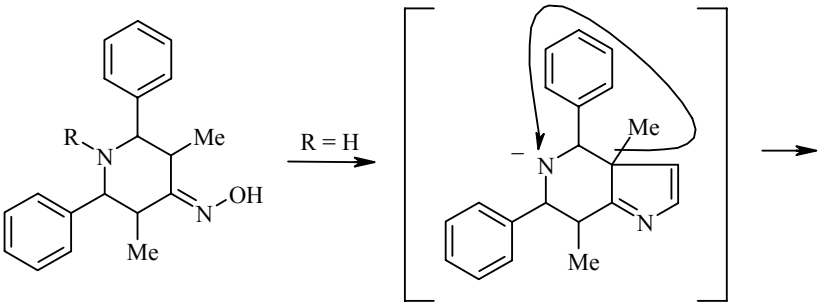
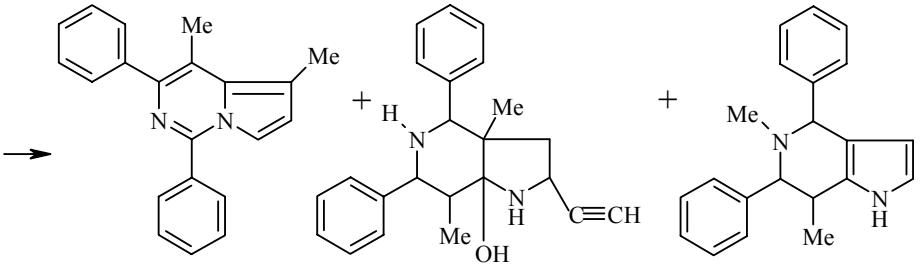
It was established by us that on heterocyclization of oxime **1** in the system RbOH–DMSO the expected tetrahydropyrrolo[1,2-*c*]pyrimidine **2** was aromatized at 70°C to pyrrolo[1,2-*c*]pyrimidine **3** [9], the presence of which was shown by TLC. In addition, under these conditions migration occurs in the intermediate compound [a 3H-pyrrole (**A**)] of the methyl group from position 3a to the anionic nitrogen atom. As a result of this 5,7-dimethyl-4,6-diphenyl-4,5,6,7-tetrahydropyrrolo[3,2-*c*]pyridine (**9**) is formed, identical with that obtained previously on heterocyclization of 1,3-dimethyl-2,6-diphenylpiperid-4-one oxime [9]. On chromatographic resolution of the reaction mixture isomers of tetrahydropyrrolo[3,2-*c*]pyridine **4** were isolated, one in the pure state, and three others as a mixture, analysis of which was carried out with the aid of chromato-mass spectrometry.



1 **A**



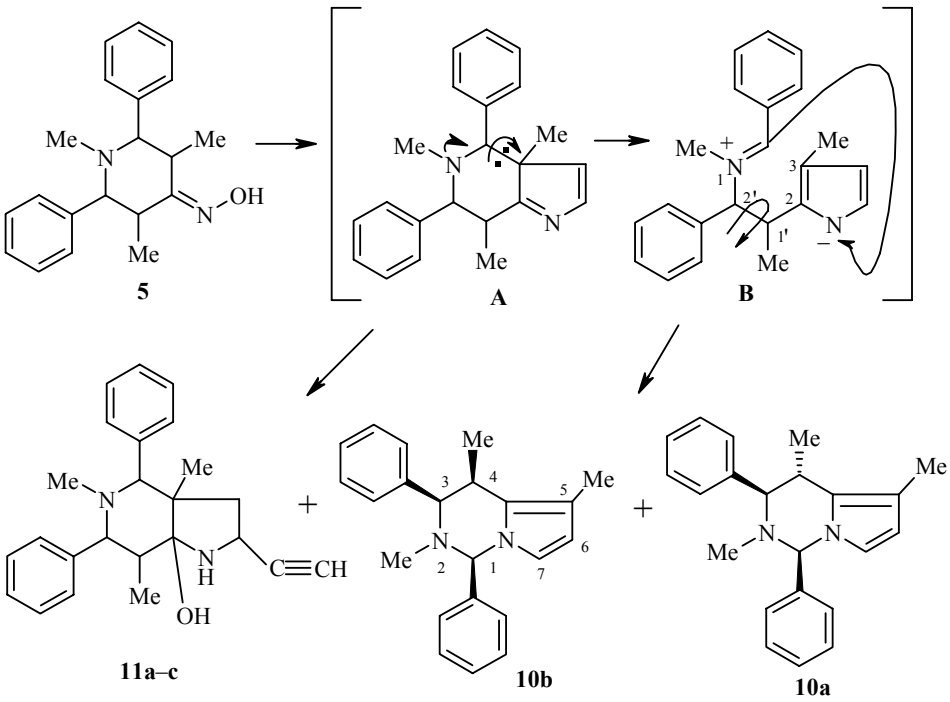
3 **4** **9**

It is logical to suggest that aromatization of the expected tetrahydropyrrolo[1,2-*c*]pyrimidine **2** in superbasic medium also occurs through the formation of an anion with the charge on a nitrogen of the tetrahydropyrimidine fragment. In order to confirm this hypothesis we studied the heterocyclization of the oxime of the pentasubstituted piperid-4-one **5** under the same conditions as for oxime **1**.

According to the data of chromato-mass spectrometry there were twenty one compounds in the reaction mixture, among which were 1,3,5-trimethyl-2,6-diphenylpiperid-4-one (28%), tetrahydropyrrolo[1,2-*c*]-pyrimidine **10** (16%), and three isomers of perhydropyrrolo[3,2-*c*]pyridine **11** (16%). The product of aromatization of compound **10**, pyrrolopyrimidine **3,** was absent from the reaction mixture (Scheme 1).

A mixture of isomeric tetrahydropyrrolopyrimidines **10a** and **10b** and an individual isomer **10b** were isolated chromatographically from the reaction mixture. The isomer **10b** has a pseudoequatorial disposition of substituents in the tetrahydropyrimidine fragment, which follows from the size of the coupling constant $^3J_{3,4} = 10.1$ Hz. In the ^{1}H NMR spectrum of compound **10b** signals were observed for all the protons in the molecule with the appropriate coupling constants. The signal of the 1-H proton was a singlet with δ 5.01, the signal of the 3-H proton was a doublet with δ 3.31, and the signal of the 4-H proton was a multiplet at δ 3.15 ppm. Analysis of the ^{1}H NMR spectrum of the mixture of isomers of **10a** and **10b** showed that in both isomers the chemical shifts of the pyrrole fragment and N-CH_3 protons coincided. The signals of the protons of

Scheme 1



the 1-, 3-, and 4-H in the spectrum of isomer **10a** have the same multiplicity as in the spectrum of compound **10b**, but were observed at 4.95, 3.84, and 3.05 ppm respectively. The size of the coupling constant $^3J_{3,4}$ = 3.7 Hz permits the assumption that in pyrrolopyrimidine **10a** the 4-CH_3 group is disposed pseudoaxially.

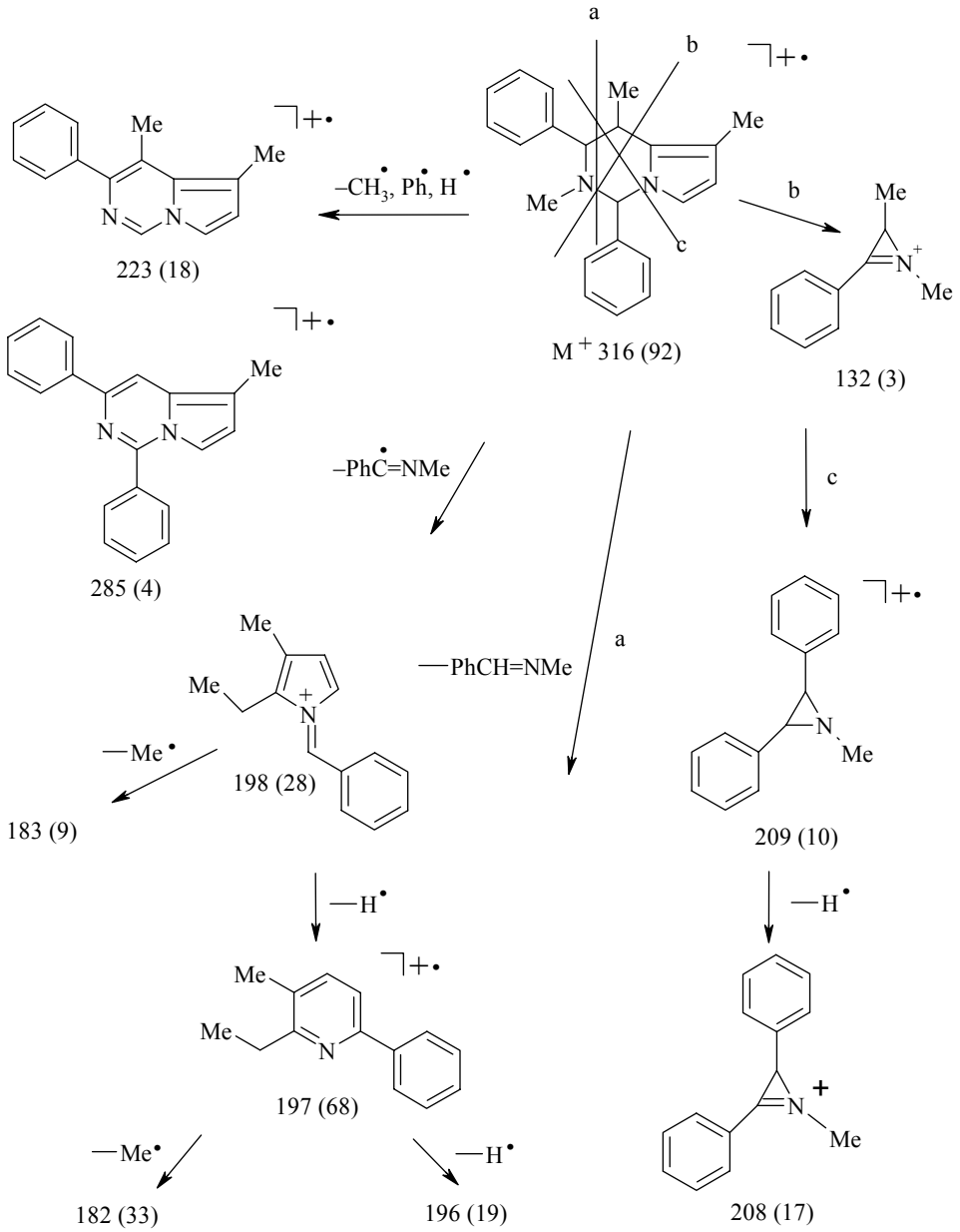
The formation of pyrrolopyrimidine **10** as a mixture of isomers and the fact that for 3,3-disubstituted 3H-pyrroles migration of a radical from position 3 to the nitrogen atom does not occur under heterocyclization conditions, shows that pyrrolopyrimidines are formed under the conditions of the Trofimov reaction as a result of a retro-Mannich reaction. This process is accompanied by aromatization of the pyrrole ring as a result of a [1,3]-sigmatropic shift. Intramolecular cyclization of the resulting zwitter-ion **B** leads to tetrahydropyrrolopyrimidine **10**. Rotation around the $C'_{(1)}$–$C'_{(2)}$ bond may occur in the process of cyclization, which is also a reason for the formation of two isomers of compound **10**.

The structures of compounds **10** and **11** were confirmed by mass spectrometry. In the mass spectrum of tetrahydropyrrolopyrimidine **10b** there was a high intensity peak for the M^+-ion, corresponding to its empirical formula. The dissociation of the molecular ion is characterized by two main breakdown pathways.

The first of these is linked with aromatization of the tetrahydropyrrolopyrimidine fragment of the molecule and is accompanied by elimination of $CH_3^{\cdot}$, $H^{\cdot}$, and $Ph^{\cdot}$ radicals in various sequences. As a result fragments with *m/z* 223 and 285 are formed, having the structure of cation-radicals of substituted pyrrolopyrimidines. The second decomposition pathway is caused by fission of the tetrahydropyrrolopyrimidine ring in three directions, *a*, *b*, and *c*. On breakdown by direction *a* fragments $[PhCH{=}NCH_3]^{+\cdot}$ [119 (16)] and $[PhC{=}NCH_3]^{\cdot}$ [118 (100)] are eliminated from the M^+-ion. As a result ions with *m/z* 197 (68) and 198 (23) are formed, which then eliminate $CH_3^{\cdot}$ and $H^{\cdot}$. Decomposition by directions *b* and *c* leads to the formation of fragment ions with the structure of a substituted aziridine and azirine (Scheme 2).

The fragmentation of N-methyl-substituted perhydropyrrolopyrimidines **11a-c** under electron impact (Table 1) is analogous to the fragmentation of N–H perhydropyrrolopyrimidines **4** [3]. As a result of their lability under electron impact conditions there are no peaks for their molecular ions in their mass spectra, but in the high mass region peaks are present for the fragment ions $[M\text{-}H_2O]^+$, which have a higher intensity than the

Scheme 2



analogous peaks in the mass spectrum of compound **3** [3]. The fragment ion 306 (2.8), observed in the mass spectrum of compound **11b**, is linked with the existence of ring-chain tautomerism and the elimination of a $NH_2C_3H_2$ particle as a result of β-fission in the ketonic form (Scheme 3).

On the basis of [3] it may be assumed that an axial-equatorial linkage of the piperidine and pyrrolidine rings occurs in compound **11b**, and there is an equatorial-equatorial linkage in compounds **11a** and **11c**.

The heterocyclization of pyrrolid-3-one oximes **6-8** with acetylene was carried out at 95°C in the system DMSO–KOH with 100 mol % of the latter. It was established by TLC in the example of oxime **7** that heterocyclization begins at a temperature of 90°C. The reaction of oximes **6-8** with acetylene was accompanied by severe resinification and the formation of a multicomponent reaction mixture, from which only unreacted oxime was successfully isolated (10-23%) by column chromatography and identified. The formation of the

TABLE 1. Peak Intensities of the Main Fragment Ions in the Mass Spectra of Perhydropyrrolopyrimidines

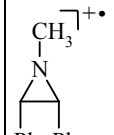
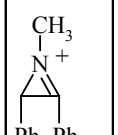
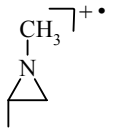
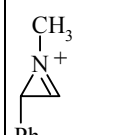
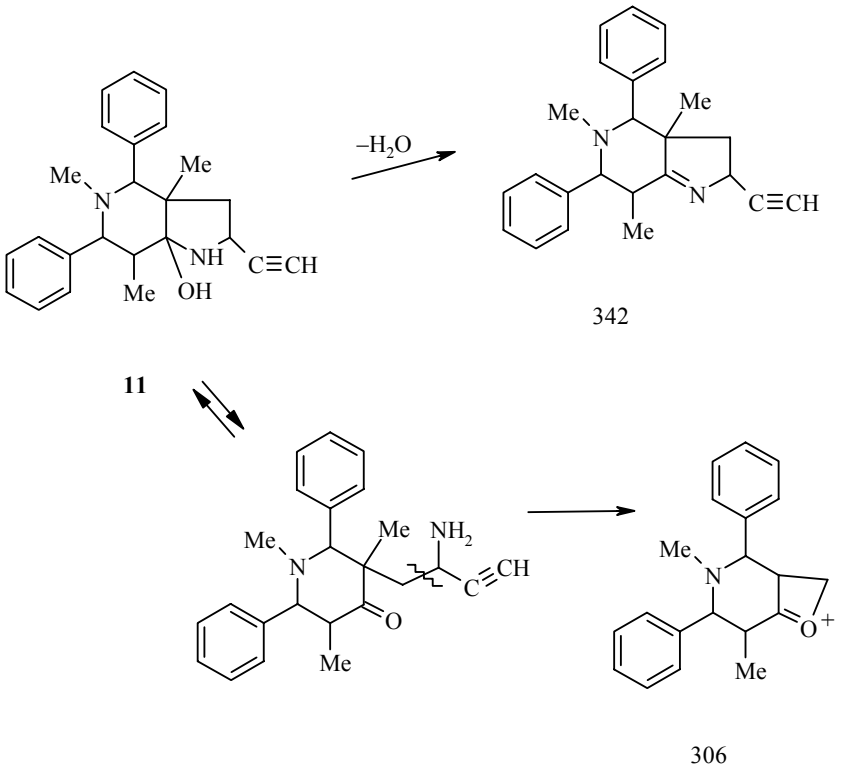
Compound	Intensity of ions, %														
	$[M-H_2O]^+$ 342	$[M-NH_2C_3H_2]^+$ 306	$[M-NH_2C_3H_2-CH_3]^+$ 291	214	 Ph Ph 209	 Ph Ph 208	 Ph 147	 Ph 146	$PhCH=N^+HCH_3$ 120	$PhCH=NCH_3^{+\bullet}$ 119	$PhC\equiv N^+CH_3$ 118	117	$PhCH_2^+$ 91	Ph^+ 77	68
11a	12.2	—	3.3	15.4	1.5	5.1	0.8	1.0	100	5.0	38.3	16.9	28.0	16.6	3.4
11b	5.9	—	1.0	9.6	2.1	3.4	0.9	1.7	100	4.0	30.8	14.1	28.8	4.8	3.3
11c	8.6	2.8	4.3	11.4	2.8	7.1	2.8	4.3	100	11.4	37.5	17.1	31.4	17.1	8.6

TABLE 2. Physicochemical Constants, Data of IR and NMR Spectroscopy, and Mass Spectroscopy of Oximes of Substituted 1-Benzylpyrrolid-3-ones **5-7**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	$[M]^+$, *m/z*	IR spectrum (KBr), cm^{-1}	NMR spectrum ($CDCl_3$), δ, ppm	Yield, %
		C	H	N					
5	$C_{11}H_{14}N_2O$	69.09 / 69.47	7.52 / 7.37	15.00 / 14.74	153-154	190	990 (N–O), 1680 (C=N) 3200-3400 (OH)	2.50-2.70 (4-H); 2.72-2.83 (5-H); 3.20 (2-H); 3.67 (CH_2Ph)	92
6	$C_{12}H_{16}N_2O$	70.42 / 70.59	7.63 / 7.84	13.65 / 13.73	78-79	204	940 (N–O), 1680 (C=N) 2850-3100 (OH)	1.34 (CH_3); 2.10-2.62 (4-H); 2.92-(-3.12) (5-H); 3.0 (2-H); 3.25 and 4.09 (CH_2Ph)	90
7	$C_{11}H_{16}N_2O$	70.08 / 70.59	7.48 / 7.84	13.58 / 13.73	150-151	204	935 (N–O), 1670 (C=N) 3200-3500 (OH)	1.23 (CH_3); 2.50-2.74 (2-H, 4-H, 5-H); 3.71 (CH_2Ph)	20

Scheme 3



expected pyrrolopyrrolidines was also not successfully shown by chromato-mass spectrometry. Probably decomposition of the pyrrolidine ring occurs in the process of heterocyclization, with a condensation reaction at the 2-CH_2 group, and also reaction at the N-benzyl radical. Decomposition of cyclic ketones containing a heteroatom in the position β to the oxime function was described in [10]. It should be noted that B. A. Trofimov and collaborators did not successfully effect heterocyclization of cyclopentanone oxime.

It has therefore been established that the formation of tetrahydropyrrolo[1,2-*c*]pyrimidines occurs by a retro-Mannich reaction under the conditions of the Trofimov reaction. It has been shown that the formation of an N-anion causes the aromatization of tetrahydropyrrolo[1,2-*c*]pyrimidines, but the Trofimov reaction may not be used for converting β-pyrrolidone oximes into pyrrolopyrrolidines.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer in KBr disks. Chromato-mass spectra were obtained on an HPMS-5988 instrument. NMR spectra were recorded on Bruker WM-400 and WP-200 spectrometers (400 and 200 MHz) at 20°C in $CDCl_3$. Aluminum oxide of Brockmann activity grade II (Fluka) was used for column chromatography, and Silufol plates for TLC. Visualization was with iodine vapor.

5,7-Dimethyl-4,6-diphenyl-4,5,6,7-tetrahydropyrrolo[3,2-*c*]pyridine (9) and 2-Ethynyl-7a-hydroxy-3a,7-dimethyl-4,6-diphenylperhydropyrrolo[3,2-*c*]pyridines (4). Acetylene was bubbled through a solution of oxime **1** (4.5 g, 15 mmol) and RbOH (0.77 g, 7.5 mmol) in DMSO (50 ml) at 70°C. After 2h, further RbOH (0.31 g, 3 mmol) was added and the reaction was conducted for 4 h (check by TLC). The mixture was cooled, poured into ice water (150 ml), and extracted with ether (5 × 100 ml). The extract was dried over $MgSO_4$. After distilling off the solvent, the residue (3.1 g) was chromatographed on a column of aluminum

oxide (1.9 × 52 cm). Initially a mixture (8 mg) of pyrrolopyrimidine **3** with 3,5-dimethyl-2,6-diphenylpiperid-4-one (R_f 0.63, ethyl acetate–hexane, 1:4) was eluted with hexane. A characteristic green spot, identical with a standard spot, appeared on TLC [3]. Then 3,5-dimethyl-2,6-diphenylpiperid-4-one (0.11 g, 3.6%) was eluted; white crystals, mp 128-130°C (hexane). A sample mixed with a standard melted with no depression of melting point. A mixture of hexane–ethyl acetate, 30:1, eluted pyrrolopyridine **9** (75 mg, 2.5%); yellow crystals, mp 126-128°C (ethyl acetate–hexane), R_f 0.64 (ethyl acetate–heptane, 1:3). Lit. data [1]: mp 128-131°C (hexane), R_f 0.63. Found, %: C 83.63; H 6.61; N 9.40. $[M]^+$ 302. $C_{21}H_{22}N_2$. Calculated, %: C 83.43; H 7.31; N 9.33. $[M]^+$ 302.

A more polar mixture of ethyl acetate–hexane, 1:10, eluted a single isomer of **4**, yellow crystals; mp 170-171°C (ethyl acetate–hexane), R_f 0.58 (Silufol, ethyl acetate–heptane, 1:3). Lit. data [3] for an isomer with an axial–equatorial linkage of rings; mp 172-173°C (hexane), R_f 0.58 (Silufol, ethyl acetate–hexane, 1:3). Found, %: N 8.34. $[M\text{-}H_2O]^+$ 328. $C_{23}H_{26}N_2O$. Calculated, %: N 8.13. $[M\text{-}H_2O]^+$ 328. Three isomers of **4** were eluted (75 mg, 2.5 %); white crystals, mp 136-145°C, R_f 0.53, 0.2, and 0.17 (Silufol, ethyl acetate–heptane, 1:3). Their chromatographic mobility was identical to a standard sample [3]. Found, %: N 8.24. $[M\text{-}H_2O]^+$ 328. $C_{23}H_{26}N_2O$. Calculated, %: N 8.13. $[M\text{-}H_2O]^+$ 328. Finally a mixture of ethyl acetate–hexane, 1:4, eluted dimethylhydroxysulfimide (80 mg); colorless crystals, mp 105-106°C (ethyl acetate–hexane). Found, %: N 15.53. $[M]^+$ 93. C_2H_7NOS. Calculated, %: N 15.05. $[M]^+$ 93.

5,7-Dimethyl-4,6-diphenyl-4,5,6,7-tetrahydropyrrolo[1,2-c]pyrimidines (10) and 2-Ethynyl-7a-hydroxy-3a,5,7-trimethyl-4,6-diphenylpyrrolo[3,2-*c*]pyridines (11). Acetylene was bubbled through a solution of oxime **5** (5 g, 16 mmol) and RbOH (0.83 g, 8 mmol) in DMSO (50 ml) at 70°C. After 2 h, further RbOH (0.4 g, 4 mmol) was added and the reaction conducted to the end (check by TLC). The mixture was cooled, poured into ice water (150 ml) , extracted with ether (5 × 100 ml), and the extract dried over $MgSO_4$. After distilling off the ether a dark resinous mass (5.14 g) was obtained. Part of this residue (2.7 g) was chromatographed on a column of aluminum oxide (1.9 × 50 cm). Initially a mixture of compounds **10a** and **10b** (20 mg, 1.32%) was eluted with hexane. NMR spectrum of compound **10a** ($CDCl_3$), δ, ppm (*J*, Hz): 1.17 (3H, d, $^3J_{CH_3}$ = 6.7, 4-CH_3); 1.75 (3H, s, N–CH_3); 2.12 (3H, s, 5-CH_3); 3.05 (1H, m, 4-H); 3.84 (1H, d, $^3J_{34}$ = 3.7, 3-H); 4.95 (1H, s, 1-H); 5.78 (1H, d, $^3J_{67}$ = 2.8, 6-H); 5.86 (1H, d, $^3J_{67}$ = 2.8, 7-H); 7.30-7.45 (10H, m, 2-C_2H_5). Pyrrolopyrimidine **10b** (35 mg, 2.3%) was then eluted, white crystals of mp 111-112°C (hexane), R_f 0.7 (Silufol, ethyl acetate–heptane, 1:2). NMR spectrum of **10b** ($CDCl_3$), δ, ppm (*J*, Hz): 1.17 (3H, d, $^3J_{CH3}$ = 6.7, 4-CH_3); 1.75 (3H, s, N-CH_3); 2.12 (3H, s, 5-CH_3); 3.15 (1H, d, $^3J_{3,4}$ = 10.1, 3-H); 3.31 (1H, m, 4-H); 5.01 (1H, s, 1-H); 5.78 (1H, d, $^3J_{67}$ = 2.8, 6-H); 5.86 (1H, d, $^3J_{67}$ = 2.8, 7-H); 7.30-7.45 (10H, m, 2-C_2H_5). Mass spectrum, *m/z* (I_{rel}, %): 316 (92) $[M]^+$, 315 (57), 302 (6), 301 (24), 288 (32), 287 (10), 286 (6), 285 (4), 240 (13), 239 (72), 224 (12), 223 (18), 210 (5), 209 (10), 208 (17), 198 (28), 197 (68), 196 (19), 194 (8), 183 (9), 182 (33), 180 (9), 167 (13), 129 (14), 128 (19), 120 (44), 119 (16), 188 (100), 116 (14), 115 (37), 91 (75), 89 (15), 82 (15), 77 (57), 65 (16), 51 (14), 42 (17). Found, %: N 8.98. $C_{22}H_{24}N_2$. Calculated, %: N 8.85. At the end of the chromatography, 1,3,5-trimethyl-2,6-diphenylpiperid-4-one (40 mg) was isolated as white crystals; mp 105-106°C (heptane). A mixing test with a standard sample gave no depression of melting point.

The reaction mixture was analyzed on the chromato-mass spectrometer. The formation of three isomers of perhydropyrrolopyridine **11** was established. The mass spectra were characterized by the presence of a peak for the $[M\text{-}H_2O]^+$ ion with *m/z* 342.

Oximes of 1-Benzyl-, 1-Benzyl-2-methyl-, and 1-Benzyl-4-methylpyrrolid-3-ones (5-7). A solution of 1-benzyl-, 1-benzyl-2-methyl-, or 1-benzyl-4-methylpyrrolid-3-ones (0.1 mol), obtained by Dieckmann cyclization from (β-ethoxycarbonylethyl)-methoxycarbonylmethylbenzylamine, (α-ethoxycarbonylethyl)-β-ethoxycarbonylethylbenzylamine, and (β-ethoxycarbonylpropyl)methoxycarbonylmethylbenzylamine respectively [8], hydroxylamine hydrochloride (0.2 mol), and potassium hydroxide (0.3 mol) in ethanol (200 ml) was boiled for 5-6 h (check by TLC). After distilling off the alcohol the residue was extracted with chloroform

(4 × 100 ml), and the extract dried over $MgSO_4$. The solid mass obtained after distilling off the chloroform was crystallized from heptane. Oximes **5-7** were obtained, the physicochemical and spectral characteristics of which are given in Table 2.

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