PYRROLO[3,2-c]PIPERIDINES

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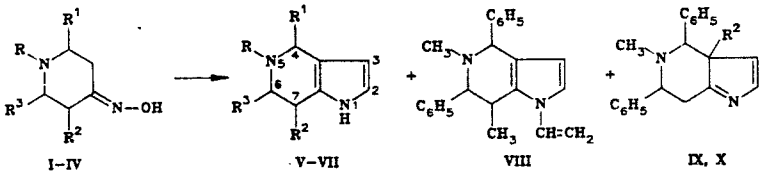
The heterocyclization reaction of oximes derived from aliphatic ketones with acetylene has been applied to piperidone oximes. Pyrrole[3,2-c]piperidines substituted on the six-membered ring have been prepared in this manner. Assumptions have been made concerning their conformational and configurational properties. These reactions have been demonstrated to lead to the formation of condensed systems containing a pyrrolenine fragment.

B. A. Trofimov and his co-workers have developed a method for the synthesis of tetrahydroindoles via the reactions of oximes derived from aliphatic ketones with acetylene in superbasic media; these reactions are of great importance in the expanding chemistry of heterocyclic compounds [1]. Since there have been no reports concerning these reactions for oximes prepared from substituted piperidin-4-ones, we have examined the properties of the compounds formed in the reactions of acetylene with oximes derived from 1,2,5-trimethyl-,2,5-dimethyl-, 1,3-dimethyl-,2,6-diphenyl-,and 1-methyl-2,3,6-triphenylpiperidin-4-ones (I-IV). Pyrrolo[3,2-c]piperidines, which may be of pharmacological interest, are formed in these reactions. Their aromatic analogs, namely, azaindoles, exhibit a wide spectrum of physiological activity [2].

In connection with the application of the Trofimov reaction to piperidone oximes, it was necessary to clarify the influence of the piperidine nitrogen atom on the reaction course as well as on the structures of the resulting products.

The heterocyclization reactions were carried out in KOH—DMSO at 90-100°C for 4-5 h.



I, III—V, VII $R=CH_3$; II, VI $R=H$; I, II, V, VI $R^1=CH_3$, III, IV, VII $R^1=C_6H_5$; I—III, V—VII, IX $R^2=CH_3$, IV, X $R^2=C_6H_5$; I, II, V, VI $R^3=H$, III, IV, VII $R^3=C_6H_5$

Ketoximes I and II led to the formation of 4,5,7-trimethylpyrrolo[3,2-c]piperidine (V) (22% yield) and 4,7-dimethylpyrrolo[3,2-c]piperidine (VI) (16% yield), respectively. Two geometric isomers are theoretically possible for these pyrrolopiperidine products. Both of these compounds could be isolated in the form of colorless crystalline substances by distillation, and they were found to consist of only one of the possible isomers.

The PMR spectra of compounds V and VI (Table 1) show, in addition to the signals for the piperidine ring protons, the presence of signals corresponding to the pyrrole fragment: a broad NH proton signal at 8 ppm, and two triplets for the 3-H and 2-H protons, associated with equal values of three spin-spin coupling constants, $J_{23} = J_{12} = J_{13} = 3$ Hz.

The observation that the cis- and trans-coupling constants for the 6-H_a protons are large, and that for the 6-H_e protons the trans-coupling constant is large and the cis-coupling constant small, indicates that the methyl group in position 7 occupies an equatorial orientation. If one assumes that in the starting materials for the synthesis of oximes I and II, namely, 1,2,5-trimethyl- and 2,5-dimethylpiperidin-4-ones, the predominant isomers

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TABLE 1. PMR Spectra of Pyrrolopiperidines (V-X) ($CDCl_3$, TMS)

Compound	Chemical shifts, δ, ppm (J, Hz)							
	NH	2-H	3-H	4-H	6-H_a	6-H_e	7-H_a*	other protons
V	8,0 br s	6,60 t (3,0)	5,98 t (3,0)	3,20 q,d (6,0; 2,0)	2,22 d,d (10,5; 9,5)	2,95 d.d (10,5; 5,0)	3,08 m	1,15 d; 1,36 d.; 2,43 s; CH_3
VI	8,3 br s	6,60 t (3,0)	6,0 t (3,0)	3,95 q,d (6,0; 1,5)	1,93 d,d (12,0; 9,5)	3,30 d.d (12,0; 5,5)	2,90 m	1,15 d; 1,34 d; CH_3; 1,58 br s, NH
VII	7,8 br s	6,57 t (3,0)	5,53 t (3,0)	4,30 s	—	3,20 m		1,0 d; 1,85 s; CH_3; 7,2—7,6 m, C_6H_5×2
VIII	AMX type spec. 6,8; 5,0; 4,6 (9,0; 16,0; 1,0)	6,70 d (3,0)	5,40 d (3,0)	4,15 d (3,0)	—	3,10 m		1,0 d; 2,0 s, CH_3; 7,1—7,6; C_6H_5×2
IX	—	5,92 br s		5,07 s	—	3,65 t (7,2)	3,0 d (7,2)	1,86 s; 1,98 br s; ; CH_3; 7,2—7,6 m; C_6H_5×2
X	—	6,30 d (3,0)	6,10 d (3,0)	5,17 br s	—	3,1—3,8 m		1,91 s; CH_3; 7,1—7,6; C_6H_5×3

*The values for 7-H_e were not determined.

feature a trans-diequatorial distribution of the 2- and 5-methyl groups, then one would conclude that the equatorially oriented methyl group in the 7-position in compounds V and VI should be located trans- to the methyl group in position 4. The observed magnitudes of the spin–spin coupling constants also provide evidence for the half-chair conformation of the piperidine fragment in compounds V and VI.

The IR spectra of compounds V and VI contain bands at 3251 and 3191 cm^{-1}, which may be assigned to stretching vibrations of the NH and H•••N bonds, respectively, of the pyrrole ring; the spectrum of VI also contains bands at 3202 and 3167 cm^{-1} for the stretching vibrations of the NH bonds of the pyrrole and piperidine rings. Bands at 3170 and 2991 (compound V) and 3112 and 3000 cm^{-1} (compound VI) in the spectra of both of these pyrrolopiperidines are attributed to CH bonds in the pyrrole ring.

The heterocyclization reaction of the dimethyl-diphenyl substituted oxime III proceeds with much more difficulty and less uniformity. The following compounds were isolated chromatographically from the reaction mixture in low yields: 5,7-dimethyl-4,6-diphenylpyrrolo[3,2-c]piperidine (VII) (4% yield), 5,7-dimethyl-1-vinyl-4,6-diphenylpyrrolo[3,2-c]piperidine (VIII) (7% yield), and 3aH,3a,5-dimethyl-4,6-diphenylpyrrolo[3,2-c]piperidine (IX) (2% yield).

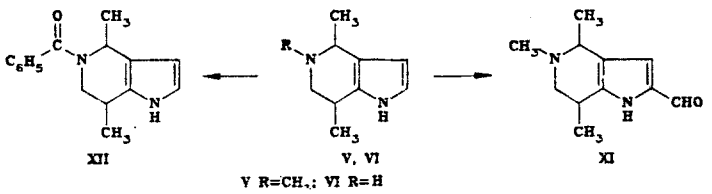
The formation of condensed systems containing a pyrrolenine fragment has been observed previously in these types of reactions. In analogy with an earlier study [3], it can be assumed that 3aH-2-hydroxy-2,3-dihydropyrrolo[3,2-c]piperidine, which is formed as a result of cyclization at the methine group of the piperidine ring, is an intermediate in the synthesis of compound IX.

The heterocyclization reaction of the triphenyl-substituted oxime IV proceeds with even more difficulty. Only 3aH-5-methyl-3a,4,6-triphenylpyrrolo[3,2-c]piperidine (X) could be isolated, in extremely low yield, from this product mixture.

The downfield portion of the PMR spectra of compounds IX and X does not contain any signals due to pyrrole-type NH protons. Because of the absence of a proton on the pyrrole nitrogen atom, the 2-H and 3-H proton signals appear as doublets with J_{23} = 3 Hz.

Heterocyclization reactions of ketoximes derived from piperidin-4-ones with acetylene in KOH–DMSO do not occur to any practical extent at temperatures lower than 90°C. Also, just as was observed in the case of cyclohexanone oxime [4], the heterocyclic ketoximes do not undergo cyclization when dioxane is used as the solvent. Heterocyclization reactions involving piperidone oximes are accompanied by a significant amount of resinification, expecially in the case of the α,α'-diphenyl substituted oximes III and IV. This is apparently associated with extensive activation of the α,α'-positions of the piperidine ring to nucleophilic attack as a consequence of the electronic effects of the phenyl substituent radicals.

Conclusive evidence for the structures of the products obtained by heterocyclization is provided by the following independent synthesis. 4,5,7-Trimethyl-2-formylpyrrolo[3,2-c]-piperidine (XI) was obtained in high yield by Villsmaier formylation of pyrrolopiperidine V. In comparison with the PMR spectrum of the starting material V, the spectrum of compound XI exhibits a downfield shift of the 3-H proton signal, by 0.67 ppm, and the lack of a $^3J_{23}$ coupling constant; as a result, the 3-H proton signal appears as a doublet (J_{13} = 2.2 Hz).



Scotten-Baumann benzoylation of pyrrolopiperidine VI gave 4,5-dimethyl-5-benzoylpyrrolo-3,2-c piperidine (XII). The PMR spectrum of this compound is characterized by the presence of two small trans- (J_{76} = 4.2) and cis- (J_{67} = 2 Hz) spin–spin coupling constants, which are indicative of an axial orientation for the methyl group in the 7-position. Benzoylation of pyrrolopiperidine VI is thus accompanied by inversion of the piperidine ring. We have observed the same type of inversion of nitrogen-containing piperidine rings in benzoylation reactions of other substrates [5].

EXPERIMENTAL

PMR spectra were obtained on a Bruker WP-80 spectrometer using $CDCl_3$ solutions vs. TMS as internal standard. IR spectra were recorded on a UR-20 spectrophotometer using KBr, LiF, and NaCl plates, in the 400-3800 cm^{-1} region, and also using KBr pellets. Mass spectra were obtained on an MS-1303 spectrometer with direct sample introduction to the ion source at an ionizing voltage of 70 eV.

1,2,5-Trimethyl-, 2,5-Dimethyl-, 1,3-Dimethyl-2,6-diphenyl-, and 1-Methyl-2,3,6-triphenylpiperidone Oximes (I-IV). These were prepared by refluxing a mixture of piperidone, hydroxylamine hydrochloride, and sodium acetate, at molar ratios of 1:2:3, in ethanol solution for 4 h. Oxime I, mp 95-97°C (from ether). Yield 81%. IR spectrum: 3200-3092 (OH), 1671 (C=N), 946 cm^{-1} (N–O). Found: C 61.4, H 10.2, N 17.5%. $C_8H_{16}N_2O$. Calculated: C 61.5, H 10.2, N 17.9%. Oxime II, mp 115-117°C (from ether). Yield 90%. Found: C 59.0, H 10.0, N 19.8%. $C_7H_{14}N_2O$. Oxine III, mp 205-208°C (from ethanol). Yield 82%. Found: C 77.8, H 7.7, 9.3%. $C_{19}H_{22}N_2O$. Calculated: C 77.6, H 7.5, N 9.5%. Oxime IV, mp 198-200°C (from ethanol). Yield 80%. Found: C 81.0, H 6.9, N 7.7%. $C_{24}H_{24}N_2O$. Calculated: C 80.9, H 6.7, N 7.9%.

4,5,7-Trimethylpyrrolo[3,2-c]piperidine (V). Acetylene was bubbled through a solution of 3 g (19 mmole) oxime I and 1.5 g (27 mmole) of potassium hydroxide in 30 ml DMSO at 95-100°C for 4 h. The reaction was followed by TLC. The reaction mixture was then poured onto ice, extracted with ether, and dried over sodium sulfate. The mixture was concentrated to ca. 30 ml volume and cooled. The precipitate was filtered. Yield 0.7 g (22%) of pyrrolopiperidine V, which was distilled [145°C (15 mm Hg)]; mp 139-140°C. Found: C 73.0, H 9.8, N 16.8%. M^+ 164. $C_{10}H_{16}N_2$. Calculated: C 73.2, H 9.8, N 17.1%. M 164.

5,7-Dimethylpyrrolo[3,2-c]piperidine (VI). This was prepared in an analogous manner from 3 g 921 mmole oxime II to give 0.5 g (16%) of compound VI, mp 155-157°C [after distillation, 160°C (15 mm hg)]. Found: C 72.0, H 9.1, N 18.3%. M^+ 150. $C_9H_{14}N_2$. Calculated: C 72.0, H 9.3, N 18.6%. M 150.

5,7-Dimethyl-4,6-diphenylpyrrolo[3,2-c]piperidine (VII), 5,7-Dimethyl-1-vinyl-4,6-diphenylpyrrolo[3,2-c]piperidine (VIII), and 3aH-3a,5-Dimethyl-4,6-diphenylpyrrolo[3,2-c]-piperidine (IX). A solution of 5 g (17 mmole) oxime III and 1.5 g (27 mmole) of potassium hydroxide in 50 ml DMSO at 90-100°C was charged with acetylene over 5 h. The reaction mixture was poured onto ice, and the reaction products were extracted into ether and dried over sodium sulfate. After evaporation of the ether the residue (4.5 g) was subjected to column chromatography (50 × 1.5 cm) on Al_2O_3 with hexane eluent. The following were eluted in succession: compound IX, 0.17 g (4%), R_f 0.74 (hexane–ethyl acetate, 3:1), as white crystals, mp 138-140°C (from hexane). Found: C 83.5, H 6.5, N 9.4%. M^+ 302. $C_{21}H_{22}N_2$. Calculated: C 83.4, H 7.3, N 9.3%. M 302; pyrrolopiperidine VIII, 0.31 g (7%), R_f 0.58 (hexane–ethyl acetate, 3:1), white crystals, mp 113-115°C (from hexane). Found: C 83.8, H 7.2, N 8.4%. M^+ 328. $C_{23}H_{25}N_2$. Calculated: C 84.1, H 7.3, N 8.5%. M 328; pyrrolopiperidine VII, 0.1 g (2%), R_f 0.4 (hexane–ethyl acetate, 3:1), yellow crystals, mp 128-131°C from hexane. Found: C 83.5, H 6.5, N 9.4%. M^+ 302. $C_{21}H_{22}N_2$. Calculated: C 83.4, H 7.3, N 9.3%. M 302.

3aH-5-Methyl-3a,4,6-triphenylpyrrolo[3,2-c]piperidine (X). Heterocyclization of 3 g (8.4 mmole) oxime V was carried out under analogous conditions. After workup the product mixture was subjected to column chromatography (40 × 1 cm) on AL_2O_3 with hexane eluent. Based on TLC analysis, the mixture consists of three substances with R_f 0.9; 0.85, and 0.83 (hexane–ethyl acetate, 3:1). Isolated, 0.008 g (0.3%) of compound X, R_f 0.9 (hexane–ethyl acetate, 3:1) as white crystals, mp 158-160°C (from hexane). Elemental analysis was not obtained due to the small quantity isolated. Compounds with R_f 0.85 and 0.83 were isolated as a mixture (0.1g).

4,5,7-Trimethyl-2-formylpyrrolo[3,2-c]piperidine (XI). CMF (0.92 g, 12.6 mmole) was cooled to –5°C and freshly distilled phosphorus oxychloride (0.48 g, 3.2 mmole) was added dropwise, and the mixture was stirred at 20°C for 40 min. It was cooled again to –5°C and a solution of 0.26 g (1.6 mmole) pyrrolopiperidine V in 2 ml DMF was added dropwise; the mixture was stirred again at 20°C for 1 h 30 min. Ice water (30 ml) was added and the mixture was basified by the addition of 10% aqueous NaOH. The mixture was extracted into ether and dried over sodium sulfate. After removal of the ether 0.25 g (83%) of yellow crystals were obtained, which were analyzed in the form of their picrate, mp 212-214°C (from alcohol). Found: N 16.7% $C_{11}H_{16}N_2O \cdot C_6H_3N_3O_7$. Calculated: N 16.6%. IR spectrum: 1668 cm^{-1} (CO). PMR spectrum: 9.7 (1H, s, CHO); 8.9 (1H, br s, NH); 6.65 ppm (1H, d, 3-H).

4,7-Dimethyl-5-benzoylpyrrolo[3,2-c]piperidine (XII). A Suspension of 0.3 g (2 mmole) pyrrolopiperidine VI and 0.1 g (2.5 mmole) NaOH in 4 ml water was treated gradually with 0.29

g (2 mmole) of freshly distilled benzoyl chloride; the mixture was stirred for 4 h at ca. 20°C, basified with NaOH solution, and extracted with chloroform. The extract was dried over magnesium sulfate. After solvent evaporation there was obtained 0.3 g (60%) of yellow crystals, mp 187-189°C (from a mixture of heptane and ethyl acetate). IR spectrum: 1618 (*cis* $\rangle$N—C(=O)$\langle$), 1593 cm^{-1} (*trans* $\rangle$N—C(=O)$\langle$). PMR spectrum: 6.55 (1H, t, J = 2.6 Hz, 2-H) 5.77 (1H, m, J = 2.6 Hz, 3-H), 5.11 (1H, br g, J = 6.5 Hz, 4-H), 3.95 (1H, br d, J = 13.2 Hz, 6e-H), 3.37 (1H, dd, J = 13.2, 4.2, 2.8 Hz, 7-H), 1.31 (3H, d, J = 6.6 Hz, 4-CH_3), 1.09 (3H, d, J = 6.8 Hz, 7-CH_3). Found: C 75,6, H 7.2, N 10.7%. M^+ 254. $C_{16}H_{18}N_2O$. Calculated: C 75.6, H 7.1, N 11.0%. M 254.

LITERATURE CITED

1. B. A. Trofimov, A. S. Agavin, A. I. Mikhaleva, G. A. Kalabin, and E. G. Chebotareva, Zh. Org. Khim., 9, 2205 (1973).
2. L. X. Yakhontov, Usp. Khim., 49, 840 (1980).
3. B. A. Trofimov, S. E. Korostova, A. I. Mikhaleva, L. N. Sobenina, V. V. Shcherbakov, and M. V. Sigalov, Khim. Geterotsikl. Soedin., No. 2, 276 (1983).
4. A. I. Mikhaleva, N- VinylPyrroles [in Russian], Nauka, Moscow (1984), p. 14.
5. T. N. Borisova, N. D. Sergeeva, A. A. Espenbetov, D. S. Yufit, A. V. Varlamov, I. V. Eliseeva, and N. S. Prostatkov, Khim. Geterotsikl. Soedin., No. 9, 1200 (1986).

SYNTHESIS AND THERMAL DECOMPOSITION OF HALOGENALKOXY(THIO)-sym-TRIAZINES.

12.* SYNTHESIS AND CERTAIN TRANSFORMATIONS OF 2-DIALKYLAMINO-4-OXO-6-CYANODIHYDROTHIAZOLO-sym-TRIAZINES

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2-(2-Chloro-2-cyanoethylthio)-sym-triazines were synthesized by reacting mercapto-sym-triazines with 2,3-dichloropropionitrile in the presence of alkali and with 2-chloroacrylonitrile. Their rearrangement—cyclization leads to 2-dialkylamino-4-oxo-6-cyano-dihydrothiazolo-sym-triazones.

It has already been shown that 2-(2-chloroethylthio)-4-methoxy-6-dialkylamino- and also 2-(2-chloroethoxy)-4-methylthio-6-dialkylamino-sym-triazines rearrange during thermolysis into dihydrothiazolo-sym-triazines [1, 2].

The aim of the present work was to establish the path of the above reaction using as examples isomeric chlorocyanoethyl derivatives, whose cyclization would lead to cyanodihydrothiazolo-sym-triazines. They are not only of interest as physiologically active compounds, but can also serve as convenient starting compounds for the synthesis of new functionally substituted dihydrothiazolo-sym-triazines.

The above chlorocyanoethylthio derivatives can be obtained by reacting mercapto-sym-triazines with 2,3-dichloropropionitrile in the presence of alkali and by their chlorocyanoethylation by 2-chloroacrylonitrile. It was found that in both cases not isomeric, but identical compounds, 2-(2-chloro-2-cyanoethylthio)-sym-triazines, are obtained. Bearing in mind the pronounced tendency of 2,3-dichloropropionitrile to undergo dehydrochlorination reactions by the action of alkaline reagents [3], it can be assumed that in the reaction of mercapto-sym-triazines with this halogenonitrile in the presence of an alkali, first a dehydrochlorina-

*For communication 11, see [7].

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