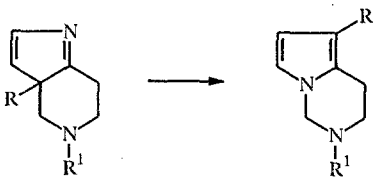
SYNTHESIS AND RECYCLIZATION OF 6-BENZYL-3a,4,5,6,7,7a-HEXAHYDRO-3a-HYDROXY-7a-METHYL-2-THIOXO-5-PHENYLOXAZOLO[5,4-c]PYRIDINES

G. V. Pshenichnyi and V. A. Mashenkov

The corresponding oxazolo[5,4-c]pyridines were obtained in the reaction of stereoisomeric 1-benzyl-3-hydroxy-3-methyl-6-phenyl-4-piperidines with potassium thiocyanate in acetic acid and rearranged into 6-benzyl-5,6,7,8-tetrahydro-1-methyl-3-thioxo-7-phenyloxazolo[3,4-c]pyrimidine by boiling in o-xylene. It was shown that the rearrangement is reversible.

When 4-piperidones react with phenylhydrazine [1, 2] and their oximes react with acetylene [3], compounds containing a pyrrolo[3,2-*c*]pyridine fragment are formed and rearranged into pyrrolo[1,2-*c*]pyrimidines in the case of R = alkyl.



In our opinion, migration of the aminomethylene unit to the exocyclic nitrogen atom in such systems is universal. This hypothesis was confirmed in a special example by conversion of 3*a*,4,5,6,7,7*a*-hexahydro-3*a*(α)-hydroxy-6,7*a*(α)-dimethyl-2-thioxo-5(α)phenyloxazolo[5,4-*c*]pyridine into 5,6,7,8-tetrahydro-1,6-dimethyl-3-thioxo-7-phenyloxazolo[3,4-*c*]pyrimidine [4].

The possibility of conducting this rearrangement with different coupling of oxazole and piperidine rings and its reversibility were investigated in the present study.

The reaction of α-ketols with potassium isocyanate and thiocyanate is one method of constructing an oxazole ring [5]. We obtained oxazolo[5,4-*c*]pyridines III and IV by reacting 3-hydroxy-4-piperidones I and II [6] with potassium thiocyanate in acetic acid. This conversion probably takes place by addition of a piperidone hydroxyl group to thiocyanic acid with formation of an intermediate thiocarbamate [7] and subsequent intramolecular addition at the carbonyl group. The proposed mechanism of the reaction is in good agreement with the high stereoselectivity of the process, since the formation of products with *cis*-coupling of the rings is more probable in synthesis of condensed bicyclic compounds by constructing a five-member ring by intramolecular addition at a carbonyl group.

The structure of synthesized compounds III and IV was confirmed by the data from elemental analysis and the IR, ^1H and ^{13}C NMR spectra. Absorption bands of stretching vibrations of O—H and N—H bonds were distinguished in the IR spectra. The protons of the piperidine ring in the PMR spectra appear as two spin systems AMX and AX, whose analysis in the case of compound III indicates a chair conformation. The SSCC between protons at $C_{(4)}$ and $C_{(5)}$ in compound IV indicate an axial orientation of the phenyl substituent, which suggests a boat conformation of the piperidine ring stabilized by an intramolecular hydrogen bond.

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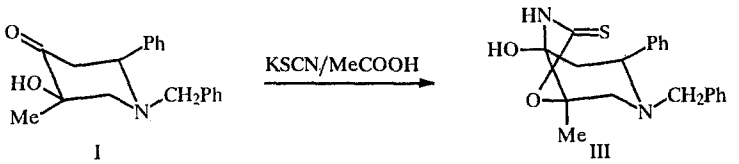
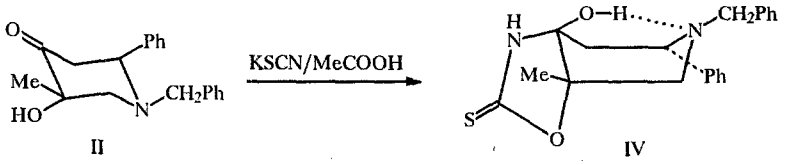
TABLE 1. Characteristics of Synthesized Compounds III-V*

Compound	Empirical formula	Mp, °C	IR spectrum, ν, cm^{-1}	^1H NMR spectrum, δ, ppm (J, Hz)	^{13}C NMR spectrum, δ, ppm	Yield, %
III	$C_{20}H_{22}N_2O_2S$	171...172	3580, 3435	1,50 (s, 7a-CH_3); 2,21 (d.d, 4-H_a; 14,0; 11,0); 2,24 & 3,03 (two d, 7-CH_2; 11,5Hz); 2,39 (d.d, 4-H_e; 14,0; 2,5); 2,84 & 3,72 (two d $\underline{CH_2}$Ph; 13,5); 3,48 (d.d, 5-H; 11,0; 2,5); 7,08...7,50 (m, 10 H_{arom}); 8,74 (s, NH)	17,4 (q, CH_3); 42,5 (t, $C_{(4)}$); 58,6 (t, $\underline{CH_2}$Ph); 61,0 (t, $C_{(7)}$); 66,5 (d, $C_{(5)}$); 89,0 & 89,8 (two d, $C_{(3a)}$ and $C_{(7a)}$); 127,3...130,0 (m, C_{arom} 140,0 & 143,4 (two s, C_{arom}); 190,5 (s, $C_{(2)}$)	73
IV	$C_{20}H_{22}N_2O_2S$	158	3585, 3440	1,31 (s, 7a-CH_3); 2,15 (d, 4-H_e; 14,5); 2,38 (d.d, 4-H_a; 14,5; 9,5); 2,57 & 2,95 (two d, 7-CH_2; 13,5); 3,13 & 3,84 (two d, $\underline{CH_2}$Ph; 13,8); 3,87 (d, 5-H; 9,5); 4,06 (s, CH); 7,12...7,41 (m, 10 H_{arom} NH)	18,1 (q, CH_3); 38,4 (t, $C_{(4)}$); 57,8 (t, $C_{(7)}$); 59,3 (t, $\underline{CH_2}$Ph); 63,6 (d, $C_{(5)}$); 88,2 & 91,5 (two s, $C_{(3a)}$ & $C_{(7a)}$); 127,4...130,0 (m, C_{arom}; 139,5 & 146,3 two s, C_{arom}); 188,9 (s, $C_{(2)}$)	90
V	$C_{20}H_{20}N_2OS$	174...175	1685	2,23 (s, CH_3); 2,93...3,09 (m, 8-CH_2); 3,58 & 3,63 (two d, $\underline{CH_2}$Ph; 13,8); 4,22 (d.d 7-H; $^1J + {}^2J$= 13,5); 4,56 & 4,65 two d, 5-CH_2; 12,5); 7,22... 7,47 (M, 10 H_{arom})	10,0 (q, CH_3); 18,7 (t $C_{(8)}$); 52,8 (t, $\underline{CH_2}$Ph); 57,4 (d, $C_{(7)}$); 62,9 (t, $C_{(5)}$); 119,4 (s, $C_{(1)}$); 127,0...129,5 (m, C_{arom}); 137,0; 138,7 & 140,5 (thr s, 2 C_{arom} & $C_{(8a)}$); 175,3 (s, $C_{(3)}$)	60

*^1H NMR spectra of III-V and ^{13}C NMR spectrum of V: solutions in $CDCl_3$; ^{13}C NMR spectra of III, IV: solutions in CD_3COCD_3.

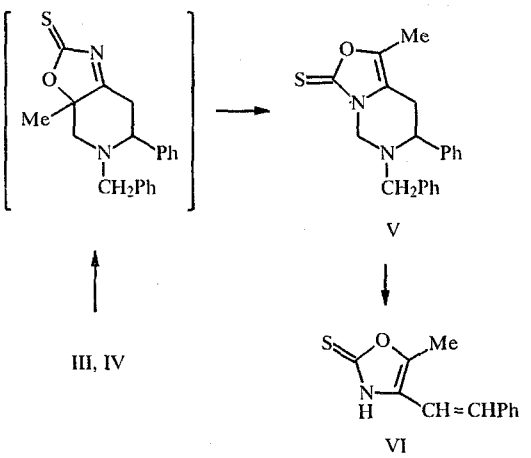


I III



II IV

We found that when oxazolo[5,4-*c*]pyridines III and IV are boiled in *o*-xylene, oxazolo[3,4-*c*]pyrimidine V was formed. Its structure is confirmed by the chemical shifts of 5-CH_2 in the ^1H and ^{13}C NMR spectra, which indicate binding of the methylene unit examined with two heteroatoms [2]. The formation of compound V can be represented as the result of dehydration of compounds II and IV and subsequent 1,3-rearrangement.

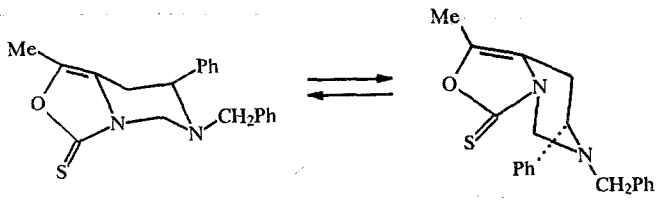


V

III, IV VI

A mixture of III and IV in the ratio of 85:15 was formed in acidification of a dioxane solution of pyrimidine V with hydrochloric acid, confirmed by the TLC and PMR spectra data, where the integral intensities of methyl protons were analyzed. Isomeric oxazoles III and IV were formed as a result of reverse rearrangement. In our opinion, the isomers appear with a 1,3-suprasurface shift due to conformational equilibrium of pyrimidine V.

When a dioxane solution of oxazolo[5,4-*c*]pyridine IV acidified with hydrochloric acid was held for 0.5 h, isomer III and compound VI appeared. Conversion of III into IV was not observed in analogous conditions. These findings are in agreement with the hypothesis concerning the mechanism of conversion of substance V into substances III and IV. It should be noted that compound VI can be obtained with a good yield in boiling of acid solutions of compounds III-V. Substance VI is an E-isomer, as the SSCC between protons at the double bond indicates.



The study thus showed that rearrangement of oxazolo[5,4-*c*]piperidines into oxazolo[3,4-*c*]pyrimidines is reversible and takes place with different coupling of oxazole and piperidine rings.

EXPERIMENTAL

The IR spectra of solutions of the substances in CCl_4 ($c = 10^{-3}$ M, $l = 1$ cm) were recorded on a Specord IR-75 spectrophotometer. The ^1H and ^{13}C NMR spectra were made on a Bruker WM-360 spectrometer, HMDS internal standard. The melting points were determined on a Boetius heated stage. The course of the reaction and purity of the compounds were monitored on Silufol UV-254 plates in benzene—acetone system, 3:1, development with iodine vapors. The characteristics of the synthesized compounds are reported in Table 1. The data from elemental analysis for C, H, and N are in agreement with the calculated data.

6-Benzyl-3*a*,4,5,6,7,7*a*-hexahydro-3*a*-hydroxy-7*a*-methyl-2-thioxo-5-phenyloxazolo[5,4-*c*]pyridine (III, IV). A. Here 8.85 g (0.03 mole) of piperidone I, II was added to 4.85 g (0.05 mole) of potassium thiocyanate in 45 ml of glacial acetic acid and left at room temperature for 18 h. The reaction mixture was neutralized with an aqueous solution of sodium carbonate, extracted with ether, dried with sodium sulfate, evaporated, and the residue was crystallized from alcohol.

B. A solution of 1 g (3 mmole) of compound V in 5 ml of dioxane was acidified with 1 ml of hydrochloric acid and held at room temperature for 0.5 h. The reaction mixture was neutralized, extracted with ether, dried, and evaporated, yielding 0.95 g (90%) of III, IV.

6-Benzyl-5,6,7,8-tetrahydro-1-methyl-3-thioxo-7-phenyloxazolo[3,4-*c*]pyrimidine (V). A solution of 1 g (2.8 mmole) of compound III, IV in 5 ml of *o*-xylene was boiled for 20 min. The precipitated crystals were filtered, washed with hexane, and dried at low pressure.

5-Methyl-4-styryl-2(3H)-thioxooxazole ($C_{12}H_{11}NOS$, VI). Here 10 ml of hydrochloric acid was added to a solution of 1 g of compound III-V in 5 ml of dioxane and boiled for 15 min. The sediment was filtered off and vacuum dried. The yield of VI was 65%. Mp = 211-215°C. IR spectrum: 3465, 1680 cm^{-1}. PMR spectrum ($CDCl_3$): 2.31 (s, CH_3); 6.94 and 7.10 (two d, C<u>H</u>=C<u>H</u>; 16.5 Hz); 7.42-7.54 ppm (5H, m, H_{arom}).

REFERENCES

1. N. F. Kucherova, L. N. Borisova, N. M. Sharkova, and V. A. Zagorevskii, Khim. Geterotsikl. Soedin., No. 9, 1219 (1970).
2. J. B. Ball, J. B. Bremner, and E. J. Browne, Heterocycles, **26**, 1573 (1987).
3. N. S. Prostakov, A. V. Varlamov, A. A. Fomichev, N. D. Sergeeva, T. N. Borisova, and Annan Khusein, in: Proceedings of the IV All-Union Conference on the Chemistry of Nitrogen-containing Heterocyclic Compounds [in Russian], Novosibirsk (1987), p. 190.
4. G. V. Pshenichnyi, Khim. Geterotsikl. Soedin., No. 6, 855 (1991).
5. R. A. Schnettler, G. P. Claxton, and W. D. J. Jones, EP No. 222,358; Chem. Abstr., **107**, 115579 (1987).
6. L. S. Stanishevskii, I. G. Tishchenko, and A. M. Zvonok, Khim. Geterotsikl. Soedin., No. 5, 670 (1975).
7. J. March, Advanced Organic Chemistry, 3rd ed., Wiley, New York (1985) [Russian translation, Vol. 3, Mir, Moscow (1987), p. 335].