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PYRIDAZINES. LIV. SYNTHESIS OF s-TRIAZOLO(2,3-b)PYRIDAZINES, A NOVEL HETEROCYCLIC SYSTEM

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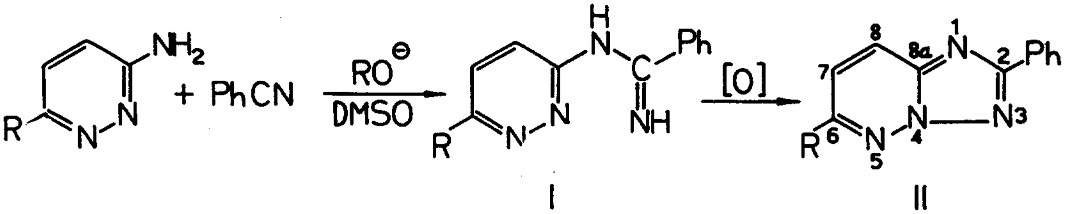
There are seven possible isomeric triazolopyridazines, but so far representatives of five systems are known.[1] We here give an account of the synthesis and some reactions of s-triazolo(2,3-b)pyridazines, a novel heteroaromatic bicyclic system.

3-Aminopyridazines, when condensed with phenyl cyanide in the presence of potassium tert-butoxide or sodium methoxide in dimethylsulfoxide afforded the corresponding amidines (I). 3-Amino-6-chloropyridazine reacted in the presence of sodium methoxide with simultaneous displacement of the chlorine atom to give I (R = OMe). The amidines could be cyclized into II either with lead tetraacetate in methylene chloride or with bromine in a solution of potassium hydroxide. The products (II) were purified by thin-layer chromatography on silica (chloroform and methanol, 10:1, as solvent). The nmr data are presented in Table I and are in accord with the proposed structures.



Total and frontier π-electron densities for the parent system, calculated by the simple HMO method[2] (Table II), predict a low reactivity towards electrophilic substitution and susceptibility for nucleophilic attack at positions 6 and/or

Table I

Compound	M.p.(°C)	Nmr data (in DMSO-d_6):τ (multiplicity,proton), J
II, R = H[a)]	131-132	1.75 (dd, H_6), 3.05 (dd, H_7), 2.05 (dd, H_8), 2.70, 1.75 (m, C_6H_5); $J_{6,7}$ = 4.0, $J_{6,8}$ = 1.5, $J_{7,8}$ = 9.4 Hz
II, R = Cl	174-175	2.35 (d, H_7), 1.62 (d, H_8), 2.60, 1.90 (m, C_6H_5), $J_{7,8}$ = 9.0 Hz
II, R = OCH_3	172-173	2.75 (d, H_7), 1.75 (d, H_8), 2.75, 1.80 (m, C_6H_5), 6.00 (s, OCH_3); $J_{7,8}$ = 9.2 Hz
II, R = $NHNH_2$	199-200	3.00 (d, H_7), 2.10 (d, H_8), 2.55, 2.00 (m, C_6H_5), 5.6 (broad, NH); $J_{7,8}$ = 9.3 Hz
II, R = N_3	210 - 214	2.76 (d, H_7), 1.67 (d, H_8), 2.55, 1.90 (m, C_6H_5); $J_{7,8}$ = 9.2 Hz
VI, X = O	>330 (dec.)	at 111°: 2.90 (d, H_7), 1.87 (d, H_8), 2.55, 1.90 (m, C_6H_5), 5.5 (broad, NH); $J_{7,8}$ = 9.4 Hz
VII	195-199	0.80 (dd, H_6), 1.75 (dd, H_7), 0.95 (dd, H_8), 2.30 (m, C_6H_5), 5.90 (s, CH_3); $J_{6,7}$ = 4.5, $J_{6,8}$ = 1.5, $J_{7,8}$ = 9.0 Hz
VIII	320-321	at 111°: 2.43 (d, H_4), 2.75 (d, H_5), 2.60, 1.95 (m, C_6H_5), 3.5 (broad, NH); $J_{4,5}$ = 9.5 Hz

a) in $CDCl_3$

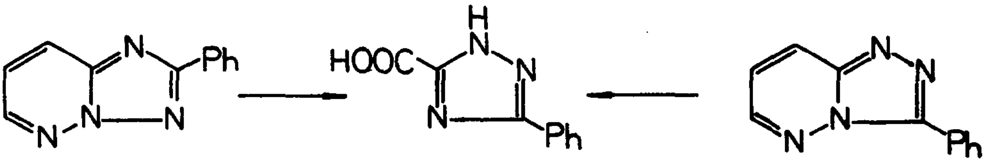
Table II

	1	2	3	4	5	6	7	8	8a
A	1.3232	0.9376	1.2937	1.5245	1.1290	0.9522	0.9572	0.9551	0.9275
B	0.2375	0.0019	0.2637	0.0027	0.1923	0.0140	0.1377	0.1345	0.0158

A = Total
B = Frontier

8. In order to examine the reactivity of this system some reactions were performed.

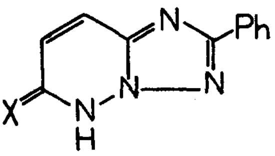
When 2-phenyl-s-triazolo(2,3-b)pyridazine (III) was oxidized with aqueous potassium permanganate at 60°, 3-phenyl-1,2,4-triazole-5-carboxylic acid (IV) was isolated and identified. The same acid was obtained by oxidizing the isomeric 3-phenyl-s-triazolo(4,3-b)pyridazine (V). As anticipated, the chlorine atom in



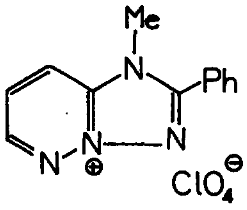
III IV V

II(R = Cl) could be displaced with nucleophiles and the corresponding ethoxy (II, R = OEt), oxo (VI, X = O) or hydrazino (II, R = $NHNH_2$) derivatives were obtained. Since a direct nucleophilic displacement of the chlorine atom with sodium azide failed, the azido compound (II, R = N_3) could be prepared by nitrosation of the hydrazino derivative. In solid state, the compound exists in the azido form as evidenced from a strong azido absorption band at 2128 cm^{-1} which parallels the observations made in the case of a 6-azido group in imidazo(1,2-b)pyridazines,[3] s-triazolo(4,3-b)pyridazines,[3,4] and tetrazolo(1,5-b)pyridazines.[4,5] Also in a solution of dimethylsulfoxide only one form is present. Reduction of the azido compound with hydrogen sulfide in hot ethanolic solution gave the corresponding 6-amino derivative (II, R = NH_2, m.p. 195-196°). In the Staudinger reaction,[6] typical for most covalent azides, the azido compound reacted with triphenyl phosphine in chloroform to give the corresponding iminophosphorane (II, R = $Ph_3P{=}N$, m.p. 243-246°).

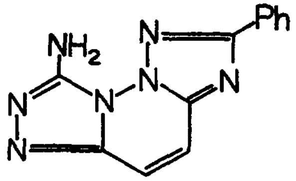
When heated with dimethyl sulfate, 2-phenyl-s-triazolo(2,3-b)pyridazine was transformed into its 1-methyl quaternary compound (VII), isolated in the form of the perchlorate salt. The chloro analog (II, R = Cl) reacted with malononitrile in the presence of potassium hydroxide in dimethylsulfoxide to give the corresponding dicyanomethylene derivative [VI, X = $C(CN)_2$; m.p. 235-240°, ir: 2183 and 2151 (CN), 3401 cm^{-1} (NH)]. Finally, a derivative of s-triazolo(2,3-b)-s-triazolo(3,4-f)pyridazine (VIII) could be prepared in a reaction between the hydrazino compound (II, R = $NHNH_2$) and cyanogen bromide at room temperature.*



VI



VII



VIII

In all of these transformations it appears that the novel bicyclic system possesses similar reactivity the isomeric s-triazolo(4,3-b)pyridazine and other related heteroaromatic azoloazines.

References

1. Compounds, pertaining to the following systems are known: s-triazolo(4,3-b)-, s-triazolo(1,2-a)-, v-triazolo(4,5-d)-, v-triazolo(4,5-c)- and v-triazolo(1,5-b)pyridazine.
2. Parameters for LCAO calculations were taken from A. Streitwieser "Molecular Orbital Theory for Organic Chemists", J. Wiley, New York, 1961, p.135.
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