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Note

Pyridazines LII. Polychloro Pyrido(2,3-*d*)- and -(3,4-*d*)pyridazines

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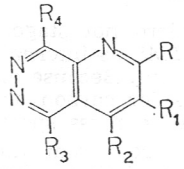
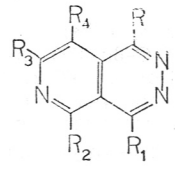
The successful synthesis of perchloroimidazo(1,2-*b*)pyridazine[1] prompted us to investigate the possibility of preparing chlorinated pyridopyridazines. Although both parent bicyclic systems (I, II) are not expected to be susceptible to electrophilic substitution, pyrido(2,3-*d*)pyridazine, when brominated, formed primarily a complex which upon pyrolysis at 170—180° is transformed into the 3-bromo derivative[2].

5,8-Dichloropyrido(2,3-*d*)pyridazine (I, $R = R_1 = R_2 = H$, $R_3 = R_4 = Cl$) when chlorinated with excess of phosphorus pentachloride afforded in dependence of reaction temperature* and time the corresponding 3,5,8-trichloro, 2,3,5,8-tetrachloro or 2,3,4,5,8-pentachloro derivatives. The facility of introduction of a chlorine atom in the pyridine part of this nucleus decreases thus in the order $3 \gg 2 \gg 4$. In a similar manner, 1,4-dichloropyrido(3,4-*d*) pyridazine (II, $R = R_1 = Cl$, $R_2 = R_3 = R_4 = H$) afforded with increasing



I



II

temperature the 1,4,8-trichloro, 1,4,7,8-tetrachloro or 1,4,5,7,8-pentachloro derivative revealing thus the following sequence of substitution $8 \gg 7 \gg 5$. The structural assignement of all products is substantiated on the basis of NMR spectra (Table I).

All polychloro pyridopyridazines are very reactive and they decompose upon atmospheric exposure. This may be anticipated when taking into account that the rate of nucleophilic substitution increases with the number of nitrogen atoms in the naphthalene skeleton and that even 5- or 8-chloropyrido(2,3-*d*)pyridazine decompose on standing on air to give a solid of undetermined structure[5]. Therefore, an attempt to displace selectively the halogen atoms with nucleophiles proved to be unsuccessful and a mixture

* Phosphorus pentachloride decomposes at heating to phosphorus trichloride and chlorine, dissociation beginning at 157—158°[3] and at about 300° the dissociation is almost complete[4].

TABLE I

NMR Data for Polychloropyridopyridazines (in $CDCl_3$)

Compound	Chemical shifs (τ)			Coupling constants (Hz)		
	H_2	H_3	H_4	$J_{2,3}$	$J_{3,4}$	$J_{2,4}$
I, R = R_1 = R_2 = H, R_3 = R_4 = Cl	0.73 (dd)	2.10 (dd)	1.48 (dd)	4.5	8.3	1.4
I, R = R_2 = H, R_1 = R_3 = R_4 = Cl	0.95 (d)		1.48 (d)			2.0
I, R = R_1 = R_3 = R_4 = Cl, R_2 = H			1.47 (s)			
	H_5	H_7	H_8	$J_{5,7}$	$J_{5,8}$	
II, R = R_1 = Cl, R_2 = R_3 = R_4 = H	0.45 (d)	0.95 (dd)	2.08 (dd)	0.8	5.8	
II, R = R_1 = R_4 = Cl R_2 = R_3 = H	0.53 (d)	1.00 (d)		0.8		
II, R = R_1 = R_3 = R_4 = Cl R_2 = H	0.51 (s)					

of different products was formed. Only with an excess of such reagents, for example with sodium methylate, uniform products were formed and in tetra- and pentachloropyrido(2,3-*d*)pyridazine all chlorine atoms, except that on position 3, were displaced.

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. NMR spectra were taken on a JEOL JNM-C-60 OHL spectrometer (TMS as internal standard) and mass spectra were recorded on a CEC 21-110 C instrument. Because of difficulties encountered when analyzing the polychloro compounds for carbon and hydrogen content, the products were characterized by high resolution mass spectra.

5,8-Dichloropyrido(2,3-*d*)pyridazine was prepared from the corresponding dihydroxy compound as described earlier[6-8] and a similar procedure was used for the synthesis of 1,4-dichloropyrido(3,4-*d*)pyridazine[6,9].

*3,5,8-Trichloropyrido(2,3-*d*)pyridazine* (I, R = R_2 = H, R_1 = R_3 = R_4 = Cl)

A mixture of the 5,8-dichloro compound (I, R = R_1 = R_2 = H, R_3 = R_4 = Cl) (0.2 g.) and phosphorus pentachloride (1.15 g.) was heated in a sealed tube at 200° for 2 hrs. The cooled reaction mixture was mixed with ice and immediately extracted with chloroform (25 ml.). Extraction was repeated twice and the combined extracts were dried over sodium sulfate. The solvent was evaporated *in vacuo* and the residue consisted of the trichloro compound and some dichloropyridopyridazinone. For purification, the mixture (50 mg.) was treated with chloroform (5 ml.) filtered and the residue, obtained after evaporation of the solvent, was sublimed at 130°/1 mm. Yield 68%, m. p. 162—165°. Mass spectrum: M^+ calcd. 232.9314 found 232.9290.

Anal. $C_7H_2Cl_3N_3$ calc'd.: N 17.92%
found: N 17.66%

In a likewise manner the following polychloropyridopyridazines were synthesized:

*2,3,5,8-Tetrachloropyrido(2,3-*d*)pyridazine* (I, $R_2 = H$, $R = R_1 = R_3 = R_4 = Cl$)

Reaction temperature was 270—280° and reaction time 3 hours. The product after sublimation at 120°/1 mm (yield 87%) had m. p. 108—110°. Mass spectrum: M^+ calc'd. 266.8924, found 266.8918.

Anal. $C_7HCl_4N_3$ calc'd.: N 15.63%
found: N 15.87%

*2,3,4,5,8-Pentachloropyrido(2,3-*d*)pyridazine* (I, $R = R_1 = R_2 = R_3 = R_4 = Cl$)

It was obtained at 285—290° for 6 hours. Upon sublimation at 130°/1 mm the pure compound had m. p. 123—125° (76% yield). Mass spectrum: M^+ calc'd. 300.8535, found 300.8519.

*1,4,8-Trichloropyrido(3,4-*d*)pyridazine* (II, $R_2 = R_3 = H$, $R = R_1 = R_4 = Cl$)

The compound was formed at 150° for 3 hours. Sublimation at 140°/1 mm afforded the pure compound in 81% yield, m. p. 171—173°. Mass spectrum: M^+ calc'd. 232.9314, found 232.9299.

Anal. $C_7H_2Cl_3N_3$ calc'd.: N 17.92%
found: N 18.30%

*1,4,7,8-Tetrachloropyrido(3,4-*d*)pyridazine* (II, $R_2 = H$, $R = R_1 = R_3 = R_4 = Cl$)

Reaction temperature was 250° during 3 hours. M. p. 137—138° (59% yield). Mass spectrum: M^+ calc'd. 266.8924, found 266.8915.

*1,4,5,7,8-Pentachloropyrido(3,4-*d*)pyridazine* (II, $R = R_1 = R_2 = R_3 = R_4 = Cl$)

The compound was obtained at 270—280° for 3 hours. M. p. 146° (yield 56%). Mass spectrum: M^+ calc'd. 300.8535, found 300.8533.

Anal. $C_7Cl_5N_3$ calc'd.: N 13.85%
found: N 13.72%

*3-Chloro-2,5,8-trimethoxypyrido(2,3-*d*)pyridazine* (I, $R_1 = Cl$, $R_2 = H$, $R = R_3 = R_4 = OCH_3$)

A mixture of 2,3,5,8-tetrachloropyrido(2,3-*d*)pyridazine (269 mg.) and sodium methylate (from 230 mg. sodium and 10 ml. methanol) was heated under reflux for 1 h. Upon cooling and filtration the solvent was evaporated to dryness and the residue was sublimed at 120°/1 mm (yield 11%), m. p. 190—192°. Mass spectrum: M^+ calc'd.: 255.0411, found 255.0412. NMR ($CDCl_3$: $\tau = 1.75$ (s, H_4), 5.85 (m, OCH_3).

Anal. $C_{10}H_{10}ClN_3O_3$ calc'd.: N 16.44%
found: N 15.95%

*3-Chloro-2,4,5,8-tetramethoxypyrido(2,3-*d*)pyridazine* (I, $R_1 = Cl$, $R = R_2 = R_3 = R_4 = OCH_3$)

The compound was obtained from pentachloro derivative I following the above procedure in 11% yield and was sublimed at 140°/1 mm, m. p. 220—223°. Mass spectrum: M^+ calc'd. 285.0516, found 285.0508. NMR (DMSO-d_6) at 76°: $\tau = 5.95$ (m, OCH_3).

Anal. $C_{11}H_{12}ClN_3O_4$ calc'd.: N 14.71%
found: N 15.02%

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REFERENCES

1. B. Stanovnik, *Synthesis* (1971) 424.
2. D. B. Paul and H. J. Rodda, *Aust. J. Chem.* **22** (1969) 1745.
3. P. Fireman and E. G. Portner, *J. Phys. Chem.* **8** (1903/4) 500.
4. W. Nernst, *Z. Elektrochem.* **22** (1916) 37.
5. D. B. Paul and H. J. Rodda, *Aust. J. Chem.* **22** (1969) 1759.
6. D. B. Paul and H. J. Rodda, *Aust. J. Chem.* **21** (1968) 1291.
7. Y. Nitta, I. Matsuura, and F. Yoneda, *Chem. Pharm. Bull.* **13** (1965) 586.
8. W. L. F. Armarego, *J. Chem. Soc.* (1963) 6073.
9. I. Matsuura and K. Okui, *Chem. Pharm. Bull.* **17** (1969) 2266.

IZVLEČEK

Piridazini. LII. Polikloro pirido(2,3-*d*)- in -(3,4-*d*)piridazini

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V odvisnosti od reakcijske temperature in časa se 5,8-diklorpirido(2,3-*d*)piridazin in 1,4-diklorpirido(3,4-*d*)piridazin pretvorita v ustrezne trikloro, tetrakloro oziroma pentakloro derivate.

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