INVESTIGATIONS IN THE PYRIDAZINE SERIES

I. Synthesis and Nucleophilic Substitution Reactions of 3-Chloromethylpyridazine

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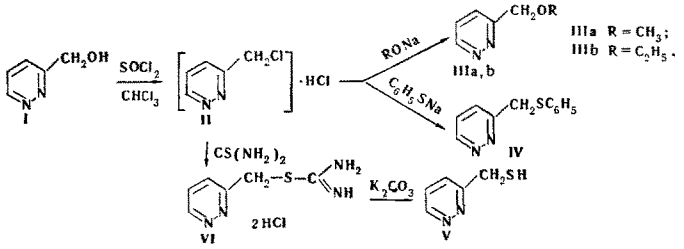
Khimiya Geterotsiklicheskikh Soedinenii, Vol. 6, No. 3, pp. 412-414, 1970

UDC 547.852.07

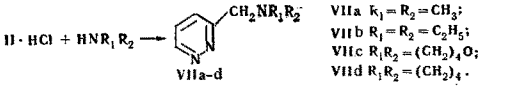
The synthesis of 3-chloromethylpyridazine hydrochloride and its reactions with nucleophilic reagents, leading to functional derivatives of pyridazine, have been studied.

The study of pyridazines substituted in the nucleus has recently been associated mainly with the search for physiologically active compounds [2–4]. Isolated examples of pyridazines containing substituents in the side chain have been studied [5, 6]. Nucleophilic substitution reactions of halogenomethylpyridazines are of undoubted interest for the synthesis of such pyridazines. Two of us have previously described the synthesis of 2-hydroxymethylpyridazine (I) from furfuryl alcohol [1]. In the present work we reacted I with thionyl chloride in chloroform to obtain 3-chloromethylpyridazine hydrochloride (II) in high (81%) yield.

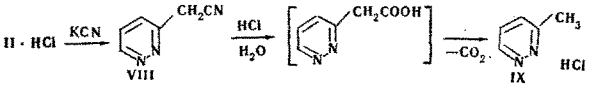
We show that the reaction of this hydrochloride with nucleophilic reagents is a convenient method for obtaining substituted pyridazines. The action of sodium methoxide or ethoxide on the hydrochloride II gave alkoxymethylpyridazines (IIIa, and b); sodium thiophenoxide gave 3-phenylthiomethylpyridazine (IV); and 3-mercaptomethylpyridazine (V) was obtained from the chloride II and thiourea with subsequent decomposition of the isothiouronium salt (VI).



On reaction with secondary amines, good yields of 3-dialkylaminomethylpyridazines (VIIa–d) were formed.



With sodium cyanide in aqueous alcohol, the chloride II forms pyridazine-3-acetonitrile (VIII). Acid hydrolysis of the nitrile VIII is accompanied by the decarboxylation of the resulting pyridazine-3-acetic acid and leads to 3-methyl-pyridazine hydrochloride (IX). We may note, for comparison, that pyridine-2-acetic acid decarboxylates in a neutral medium at 50° C [7].



EXPERIMENTAL

3-Chloromethylpyridazine hydrochloride (II). A solution of 12 g (0.1 mole) of 3-hydroxymethylpyridazine (I) in 60 ml of absolute chloroform was added to a solution of 15 ml (~0.13 mole) of thionyl chloride in 20 ml of absolute chloroform. The mixture was stirred at room temperature for 2 hr, and the upper layer was separated off and poured into acetone. The crystals that separated were filtered off and washed with a small amount of acetone. Additional amounts of II were isolated from the moter acetone by the addition of ether. This gave 14.5 g (81%) of II; mp 121–121.5° C (from ethyl acetate). Found, %: C 36.44; H 3.88. Calculated for $C_6H_5ClN_2 \cdot HCl$, %: C 36.40; H 3.66.

3-Methoxymethylpyridazine (IIIa). In drops, a solution of 3.3 g (20 mM) of the hydrochloride II in 30 ml of methanol was added to a solution of sodium methoxide prepared from 1.84 g of sodium and 30 ml of absolute methanol, and the mixture was stirred at room temperature for 30 min and in a boiling water bath for 4–5 hr. The mixture was cooled, the precipitate was filtered off, and excess ethanol was distilled off. The residue was treated with ether, and distillation yielded 1.82 g (76%) of **IIIa**; bp 114–115° C (11 mm); d_4^{20} 1.0978; n_D^{20} 1.5077. Found, %: C 57.78; H 6.61. MR_D 33.50. Calculated for $C_6H_8N_2O$, %: C 58.06; H 6.45. MR_D 32.93. **Picrate**, Mp 87–88° C (from aqueous ethanol). Found, %: C 41.14; H 3.51. Calculated for $C_6H_8N_2O \cdot C_6H_3N_3O_7$, %: C 40.83; H 3.14.

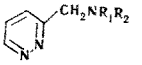
3-Ethoxymethylpyridazine (IIIb). As described above, 1.84 g of sodium, 50 ml of absolute ethanol, and 3.3 g of the hydrochloride II yielded 1.5 g (55%) of **IIIb**; bp 108–109° C (7 mm); d_4^{20} 1.0543: n_D^{20} 1.4990. Found, %: C 60.71; H 7.47. MR_D 38.77. Calculated for $C_7H_{10}N_2O$, %: C 60.85; H 7.29. MR_D 38.65. **Picrate**, mp 103–104° C (from aqueous ethanol). Found, %: C 42.64; H 3.75. Calculated for $C_7H_{10}N_2O \cdot C_6H_3N_3O_7$, %: C 42.63; H 3.56.

3-Phenylmercaptomethylpyridazine (IV). With stirring at 45–50° C, 3.3 g (0.03 mole) of thiophenol was added dropwise to a finely dispersed suspension of 0.69 g (0.03 g-at.) of sodium in 2 ml of absolute toluene, and stirring was continued for an additional 4 hr at the same temperature. A solution of the base of II in 20 ml of absolute toluene [obtained from 3.3 g (20 mM) of the hydrochloride II and 1.1 g (20 mM) of caustic potash in toluene] was added, and the mixture was heated in a boiling water bath for 2 hr and then cooled. The precipitated sodium chloride was filtered off and washed with ether, and the solvent was distilled off. The crystallized residue gave 3.9 g (96%) of **IV**; mp 54–54.5° C (from petroleum ether). Found, %: C 65.59; H 5.11; S 15.17. Calculated for $C_{11}H_{10}N_2S$, %: C 65.33; H 4.99; S 15.86. **Picrate**, mp 112–113° C (from ethanol). Found, %: C 47.59; H 3.13. Calculated for $C_{11}H_{10}N_2S \cdot C_6H_3N_3O_7$, %: C 47.34; H 3.04.

3-Mercaptomethylpyridazine (V). A solution of 2.5 g (~15 mM) of the hydrochloride II and 1.2 g (16 mM) of thiourea in 300 ml of absolute acetone was boiled for 10 hr, and the precipitate was separated off and washed with acetone. This gave 3.4 g (92%) of 3-isothioureidomethylpyridazine hydrochloride (**VI**), white crystals, mp 187–188° C (from a hexane–methanol mixture, decomp). Found, %: C 30.10; H 4.15. Calculated for $C_6H_{10}Cl_2N_4S$, %: C 29.88; H 4.18.

Potassium carbonate was added to 2.5 g of VI in 20 ml of water to saturation, the mixture was heated in a water bath for 1 hr, and then carefully extracted with hot benzene. The benzene extracts were dried with $MgSO_4$ and the solvent was distilled off to give 1.2 g (94%) of V in the form of white crystals, mp 97–98° C (from a hexane–benzene mixture). Found, %: C 47.98; H 4.51; N 22.36; S 25.39. Calculated for $C_5H_6N_2S$, %: C 47.60; H 4.79; N 22.20; S 25.41.

3-Dialkylaminomethylpyridazines (VIIa–d). With stirring, a suspension (in ether or benzene) of 0.01 mole of the hydrochloride II was added to a mixture of an ethereal ($R_1 = R_2 = CH_3$) or a benzene [$R_1R_2 = (CH_2)_4$; $(CH_2)_4O$] solution of 0.05 mole of the amine (when $R_1 = R_2 = C_2H_5$, the amine itself acted as solvent) and 0.1 mole of caustic potash, and the mixture was boiled for 3 hr and left overnight. Vacuum distillation yielded the corresponding amine. The constants and yields of the amines (and their picrates) are given in the table.

Dialkylaminomethylpyridazines 

Compound	Bp, °C (mm)	Mp, °C	Empirical formula	Found, %		Calculated, %		Yield, %
				C	H	C	H	
VIIa*	112—114(8)	—	$C_7H_{11}N_3$	60.78	8.15	61.27	8.08	74
VIIb**	124—125(6)	—	$C_9H_{15}N_3$	64.96	9.27	65.41	9.15	87
Dipicrate of VIIb		145,5—146 (from ethanol)	$C_9H_{15}N_3 \cdot 2C_6H_3N_3O_7$	40.56	3.71	40.45	3.39	
VIIc	130—131(1)	56—57	$C_9H_{13}N_3O$	59.92	7.55	60.31	7.31	85
Dipicrate of VIIc		169—170 (from ethanol)	$C_9H_{13}N_3O \cdot 2C_6H_3N_3O_7$	39.92	3.08	39.57	3.00	
VIId	115(1,5)	51—52	$C_9H_{13}N_3$	66.51	8.38	66.23	8.03	96
Dipicrate of VIId		148—149 (from ethanol)	$C_9H_{13}N_3 \cdot 2C_6H_3N_3O_7$	40.69	3.20	40.59	3.08	

*d_4^{20} 1.0112; n_D^{20} 1.5119. Literature data [6]: bp 105-106° C (7 mm); n_D^{20} 1.5133; dipicrate mp 144-144.5° C.

**d_4^{20} 0.9825; n_D^{20} 1.5042.

Pyridazine-3-acetonitrile (VIII). With stirring and heating in a water bath, 3.3 g (20 mM) of the hydrochloride II in 10 ml of ethanol was added to a solution of 3.25 g (66 mM) of sodium cyanide in 5 ml of water and the mixture was boiled for 1 hr and cooled, and the precipitate was filtered off. The ethanol was distilled off and the residue was treated with a saturated solution of sodium carbonate (50 ml) and extracted with ethyl acetate. The extract was dried with magnesium sulfate and the ethyl acetate was distilled off. The crystallized residue gave 1.1 g (46%) of the nitrile VIII; mp 90–91° C (from benzene). According to the literature [6], mp 90–91° C. Found, %: C 60.58; M 4.41. Calculated for $C_6H_5N_3$, %: C 60.50; H 4.23. A mixture with the pyridazine-3-acetonitrile that we had obtained previously [1] showed no depression of the melting point.

Hydrolysis of pyridazine-3-acetonitrile. A mixture of 1 g of the nitrile VIII and 15 ml of 10% HCl was heated at 60° C for 5 hr. The acid was distilled off in vacuo, and the solid residue was treated with absolute ethanol. After elimination of the ethanol, 1.05 g of 3-methylpyridazine hydrochloride (IX) was obtained (quantitative yield): mp 191–192° C (from acetone). A mixture with an authentic sample gave no depression of the melting point. Found, %: C 46.33; H 5.45. Calculated for $C_5H_6N_2 \cdot HCl$, %: C 46.01; H 5.36. When a mixture of 1 g of the nitrile VIII and 15 ml of 2% HCl was kept at room temperature for 3 days with subsequent elimination of HCl in vacuo, 1.2 g (93%) of pyridazine-3-acetonitrile was obtained. Mp 132–133° C (from ethyl acetate). Found, %: C 46.50; H 4.23. Calculated for $C_6H_5N_3 \cdot HCl$, %: C 46.32; H 3.89. The treatment of pyridazine-3-acetonitrile hydrochloride with potassium carbonate yielded the initial nitrile VIII, with mp 89–91° C.

REFERENCES

1. K. Yu. Novitskii, N. K. Sadovaya, and A. B. Baskina, KhGS [Chemistry of Heterocyclic Compounds], collection 2, 1970 (in press).
2. P. Coad, R. A. Coad, and B. Dubinsky, J. Med. Chem., 8, 129, 1965.
3. S. A. Hiller, É. A. Baumanis, G. P. Sokolov, and V. Ya. Grinshtein, DAN, 145, 440, 1962.
4. E. A. Steck, R. P. Brundage, and L. T. Fletcher, J. Am. Chem. Soc., 76, 4454, 1954.
5. T. Nakagome, Yakugaku Zasshi, 83, 934, 1963; C. A. 60, 5490, 1964.
6. A. Dornow and W. Abel, Ber., 97, 3349, 1964.
7. M. P. Oparina, Khim.-farm. prom., 2, 98, 1936.

24 June 1968

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