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THE PREPARATION OF SOME DIALKYL PYRIDAZINES

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The preparation of 3,4- and 4,5-dimethyl-, 3,4- and 4,5-trimethylene-, and 3,4- and 4,5-tetramethylene-pyridazine was undertaken to provide material for spectral examination. The particular reactions utilized for these syntheses are not unique and follow general techniques that have already been outlined (1–3). Nevertheless, several features merit special comment.

The reactions of the appropriately substituted anhydrides (I) (See Figure 1) with hydrazine hydrate in benzene solution were found to produce three types of compounds. Δ^1-Tetrahydrophthalic anhydride led directly to the desired cyclic hydrazide IIIc while cyclopentene-1,2-dicarboxylic anhydride yielded the half acid hydrazide IIa, both in very good yield. (Although the half-acid hydrazide IIa was not completely characterized it did dissolve with effervescense in aqueous sodium bicarbonate and lost water when heated in Nujol, yielding the cyclic hydrazide IIIa.) Under the same conditions dimethylmaleic anhydride condensed with hydrazine hydrate to form N-aminodimethylmaleimide in 80% yield along with 8% of the benzene-insoluble cyclic hydrazide IIIb. The use of ethanol as a solvent and increasing the relative quantity of hydrazine hydrate appeared to be ineffective in increasing the yield of the cyclic hydrazide. Efforts to isomerize the N-aminodimethylmaleimide by heating above the melting point in a sealed tube and by strongly basic catalysis were not very satisfactory. However a recent procedure by Mizzoni and Spoerri (2) using a strongly acidic aqueous solution was found to give the desired product (IIIb) directly and in good yield. Vaughan (4) has concluded that those phthalic acids that form anhydrides with difficulty yield the six membered (hydrazide) ring exclusively while those that form anhydrides more readily may yield either the five (imide) or six membered ring. Accordingly, dimethylmaleic anhydride would be expected to produce largely the N-aminoimide.

In the course of one experiment on the preparation of 3,6-dichloro-4,5-trimethylenepyridazine the product isolated was 6-chloro-4,5-trimethylenepyridaz-3(2)-one, rather than the expected dichloride. Apparently one of the chlorine atoms is hydrolyzed rather readily, perhaps more readily than in the case for 3,6-dichloropyridazine (3).

Reduction of the chlorodialkylpyridazines (IV and X) was accomplished with phosphorus and freshly distilled, constant boiling hydriodic acid (5). This manner of reduction, particularly when the hydriodic acid was not fresh and had discolored, was complicated by the formation of iododialkylpyridazines (VI and XII). 4-Chloropyridine (6) and 2,4-dichloro-3-cyano-6-methylpyridine and its 5-nitro derivative (7) have been shown to exchange their chlorine atoms for

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TABLE I

PREPARATION OF DIALKYL PYRIDAZINES

Compd.	Procedure	Yield, %	Solvent (Recrystn.)	M.P. (B.P.), °C.	Analysis							
					Calc'd				Found			
					C	H	N	Br	C	H	N	Br
IVa[a]	A	85	Pet. ether	83	44.5	3.2	14.8		44.7	3.2	14.8	
IVb	A	83[b]	Pet. ether	119–120	40.7	3.4			40.7	3.3		
IVc	A[c]	84	Ethanol	158.5–159			13.8				13.7	
Xa	A	60	Pet. ether	93–94	54.4	4.6			54.3	4.7		
Xb	A	60	Pet. ether	47–48	50.5	5.0			50.3	4.7		
Xc	A	65		135–137[d] (2 mm.)	57.0	5.4			57.0	4.9		
Va	B	72	Pet. ether	83–86	70.0	6.7	23.3		69.8	6.5	23.2	
Vb	B	55		58–59	66.6	7.5	25.9		66.5	7.5	26.1	
Vc	B	39[e]		88.5–89	71.6	7.5	20.9		71.3	7.4	21.1	
VIIIa	C	93	Pet. ether-benzene	130–133[f]	60.9	7.3	20.3		60.8	7.5	20.4	
VIIIb	C[g]	74	Ethanol	108–110	57.1	8.0			57.1	8.0		
VIIIc	C	75		114–115			18.4				18.2	
IXa (HBr)	D	84	Ethyl acetate	183–186	38.7	4.2			38.4	4.4		
IXa		93	Water	218–220	61.8	5.9			61.7	6.0		
IXb (HBr)	D	88	Acetic acid	183–185			13.7	39.0			13.4	38.3
IXb				230–231	58.1	6.5			57.9	6.5		
IXc (HBr)	D	82		193–199				34.6				33.5
IXc				192–194			18.7				18.9	
XIa	B	68		66–67	70.0	6.7	23.3		70.3	6.7	23.5	
XIb	B	66		33–34	66.6	7.5	25.9		66.5	7.3	25.7	
XIc	B	poor[h]		oil	71.6	7.5			71.4	7.7		
				PICRATES								
Free Base												
Va				156.5–158			20.1				19.9	
Vb				166.5–167			20.8				20.6	
Vc				167.5–168			19.3				19.5	
XIa				135–136			20.1				20.3	
XIb				174–175			20.8				20.5	
XIc				156–157			19.3				19.3	

[a] In one preparation of IVa ice was added to the mixture during neutralization. From this run there was isolated 6-chloro-4,5-trimethylenepyridaz-3(2)one, m.p. 204–207° (recryst. from benzene and sublimed). *Anal.* Calc'd for $C_7H_7ClN_2O$: N, 16.4. Found: N, 16.4. [b] Precipitated on neutralization. An additional 17% may be recovered by extraction with ether. [c] Heating period was two hours at 80–85°. The dichloride precipitated on pouring the reaction mixture onto ice. [d] Colorless oil which turned red on standing. [e] Also isolated was 11% of 3-iodo-4,5-tetramethylenepyridazine (VIc), m.p. 174–174.5° (with decomposition); *Anal.* Calc'd for $C_8H_9IN_2$: N, 10.8. Found: N, 11.1. A 50% yield of 3-iodo-4,5-trimethylenepyridazine (VIa), m.p. 141–142° dec. (3 times from ethanol) was obtained in the reduction of IVa with undistilled hydriodic acid and red phosphorus. *Anal.* Calc'd for $C_7H_7IN_2$: C, 34.2; H, 2.9; N, 11.4. Found: C, 34.1; H, 3.0; N, 11.5. [f] Several more recrystallizations raised the m.p. to 139–140°. [g] Only 8% of the described amount of ethanol was used as solvent. An additional 12% of product may be obtained by concentration of the mother liquors. [h] A 75% yield of 6-iodo-3,4-tetramethylenepyridazine, m.p. 181–183° (dec.) (from ethanol) was obtained. *Anal.* Calc'd for $C_8H_9IN_2$: N, 10.8. Found: N, 10.8.

iodine in the presence of hydriodic acid. The separation of the dialkylpyridazines (V and XI) from their iododerivatives was readily accomplished by virtue of the fact that the diazahydrocarbons are soluble in water while the iodo-compounds are not.

Two of the iodo-compounds were found to be unusual. Both 3-iodo-4,5-trimethylenepyridazine (VIa) and 6-iodo-3,4-dimethylpyridazine (XIIb) liberated free iodine while in isoöctane solution at a concentration of 1.00 g./l. This was first observed in a solution of the former (VIa) that had been standing for several weeks, while it was noticeable in the latter (XIIb) after it had been standing only a few hours.

The diazahydrocarbons (V and XI) prepared in this work were found to be somewhat unstable compounds. On standing for several days they become violet-colored, presumably due to oxidation. The colored impurity is insoluble in all of the common organic solvents and may be effectively removed by recrystallization. It was also found that samples that had been freshly sublimed became discolored more quickly than did those which had been recrystallized after sublimation, the violet color becoming apparent in less than one day. Spectral changes accompanying the decompositions will be reported later. With the exception of 6-chloro-3,4-trimethylenepyridazine (Xc) the chloro compounds, on the other hand, appear to be quite stable. On standing the former compound changed to a red oil and a crystalline material separated which was not characterized.

EXPERIMENTAL

Melting points were taken on Anschütz short-stem thermometers and are uncorrected.

Preparation of starting materials. 4,5-Disubstituted pyridazines, Fig. 1. Cyclopentane-1,2-dicarboxylic anhydride was obtained from 2-carbethoxycyclopentanone by a series of operations including addition of hydrogen cyanide, dehydration with thionyl chloride, acid hydrolysis and finally dehydration with acetic anhydride (8, 9). The same series of operations on ethyl methylacetoacetate afforded a good yield of dimethylmaleic anhydride (10), b.p. 105–110° at 12 mm. Recrystallization from pet. ether yielded colorless crystals, m.p. 92–94° (11–13). Relatively large quantities of Δ^1-tetrahydrophthalic anhydride were prepared (14) by isomerization of the *cis*-Δ^4 isomer. The distilled and recrystallized Δ^1-isomer melted at 71–72° (15) and did not depress the m.p. of a sample prepared by the method of Baeyer (16) from 2-carbethoxycyclohexanone.

3,4-Disubstituted pyridazines, Fig. 1. Ethyl 2-cyclopentanone acetate (VIIa) (b.p. 132–135° at 20 mm.) was obtained by the procedure of Schüler (17). Ethyl β-methyllevulinate (VIIb) was available by well-known methods (18, 19). Ethyl 2-cyclohexanone acetate (VIIc) was prepared by the methods used for VIIa; b.p. 131–133° at 11 mm.

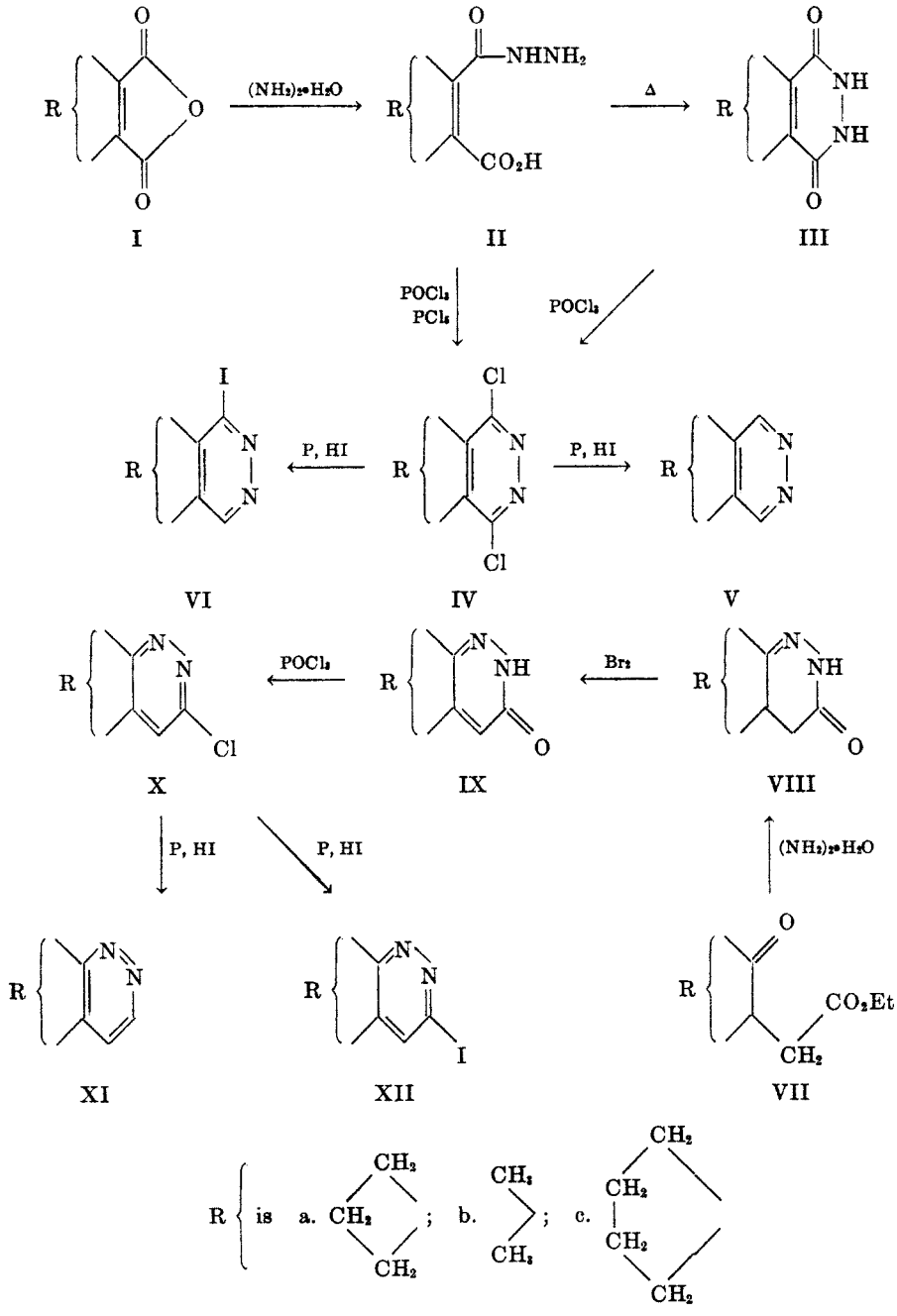
Dimethylcyclopentene-1,2-dicarboxylate. To 3.9 g. (0.025 mole) of cyclopentene-1,2-dicarboxylic acid in 40 ml. of ether was added an ethereal solution of diazomethane until the reaction no longer caused effervescence and a yellow color persisted. The color was removed with a few crystals of the dibasic acid, the ether was removed by evaporation, and the residue afforded 3.2 g. (72%) of the ester, b.p. 120–125° at 11 mm.

Anal. Calc'd for $C_9H_{12}O_4$: Mol. Wt., 184; C, 58.7; H, 6.6.

Found: Sap'n. Eq., 181; C, 58.5; H, 6.5.

N-Aminodimethylmaleimide. A 5.05-g. (0.04 mole) portion of dimethyl maleic anhydride in 100 ml. of ethanol was heated to reflux and a solution of 2.00 g. (0.04 mole) of hydrazine hydrate in 100 ml. of ethanol was added slowly with stirring. Vacuum evaporation of the

FIGURE 1



FLOW SHEET FOR THE PREPARATION OF 4,5-DIALKYLPYRIDAZINES AND 3,4-DIALKYLPYRIDAZINES

ethanol produced a nearly quantitative yield of a mixture of the isomers, N-aminodimethylmaleimide and 4,5-dimethylpyridaz-3,6(2,1)-dione (IIIb). Extraction with warm petroleum ether left a small quantity of IIIb as a residue and on cooling 4.5 g. (80%) of N-aminodimethylmaleimide separated as yellow crystals which were recrystallized from petroleum ether, m.p. 101–102°.

Anal. Calc'd for $C_6H_8N_2O_2$: N, 20.0. Found: N, 19.7.

The colorless *acetyl derivative* after three recrystallizations from water melted at 189–193°.

Anal. Calc'd for $C_7H_{10}N_2O_3$: N, 15.4. Found: 15.1.

The *benzenesulfonyl derivative* was prepared in the usual manner ans was recrystallized from ethanol, m.p. 197–199°.

Anal. Calc'd for $C_{12}H_{12}N_2O_4S$: N, 10.0. Found: N, 10.1.

Cyclopentene-1,2-dicarboxylic acid monohydrazide (IIa). A 7.40-g. (0.054 mole) portion of the anhydride Ia in 90 ml. of benzene was treated dropwise with 2.90 g. (0.058 mole) of hydrazine hydrate with stirring at reflux. After 30 minutes of reflux the yellow precipitate was removed by filtration and air-dried to yield 9.05 g., 99% of the monohydrazide. Efforts to purify a sample for analysis were unsuccessful. The acid hydrazide does not melt; on heating it loses water and sublimes to produce 4,5-trimethylenepyridaz-3,6(2,1)-dione, IIIa, in 59% yield. It is soluble in dilute bicarbonate solution while the cyclic hydrazide, IIIa, is not.

4,5-Trimethylenepyridaz-3,6(2,1)-dione (IIIa). A 3.50-g. sample of the monohydrazide IIa was heated at 225° in 100 ml. of Nujol for 20 minutes. The reaction mixture was filtered while hot and was washed several times with benzene to yield 2.95 g., 94%, of a light tan powder which was satisfactory for subsequent reactions and could be sublimed to a white powder that turns grey at 275°, m.p. 324–327°.

Anal. Calc'd for $C_7H_8O_2$: C, 55.3; H, 5.3; N, 18.4.
Found: C, 55.1; H, 5.4; N, 18.7.

The dione, IIIa, was also prepared by refluxing 1.00 g. of 1,2-dicarbomethoxycyclopentene in benzene solution with excess hydrazine hydrate for several hours, then adding xylene and evaporating to remove the excess hydrazine hydrate. IIIa separated in a crude yield of over 63%.

4,5-Dimethylpyridaz-3,6(2,1)-dione (IIIb). Following a procedure of Mizzoni and Spoerri (2), 3.3 g. (0.026 mole) of dimethylmaleic anhydride (Ib) was added to a boiling solution of 2.75 g. (0.026 mole) of hydrazine dihydrochloride in 6 ml. of water. This was heated carefully for four hours, was then cooled, filtered, washed and dried to yield 3.0 g., 85%, of colorless crystals m.p. 347–351°, discoloring at 310°.

Anal. Calc'd for $C_6H_8N_2O_2$: N, 20.0. Found: N, 19.7.

Compound IIIb was also prepared in 50% yield by isomerizing 5.60 g. of N-aminodimethylmaleimide with 50 ml. of sodium ethoxide, prepared from 1.5 g. of sodium, at reflux for four hours, cooling and filtering.

4,5-Tetramethylenepyridaz-3,6(2,1)-dione (IIIc). This was prepared in the same manner as cyclopentene-1,2-dicarboxylic acid monohydrazide (IIa), and was recrystallized from ethanol to produce fine, colorless crystals, m.p. 295–298°, in 76% yield.

Anal. Calc'd for $C_8H_{10}N_2O_2$: C, 57.8; H, 6.1.
Found: C, 57.9; H, 5.9.

3,6-Dichloro-4,5-trimethylenepyridazine (IVa). *Procedure A.* A 2.55-g. (0.017 mole) portion of 4,5-trimethylenepyridaz-3,6(2,1)-dione (IIIa) was treated with 25 ml. of phosphorus oxychloride at 80° for one-half hour. The reaction mixture was poured on ice, neutralized with concentrated aqueous sodium hydroxide with efficient external cooling, and extracted with ether. The ether was evaporated and the residue was recrystallized from petroleum ether to yield 2.70 g., 85%, of IVa as colorless needles, m.p. 79–80°. The m.p. was raised to 83° by recrystallization from petroleum ether.

Anal. Calc'd for $C_7H_6Cl_2N_2$: C, 44.5; H, 3.2; N, 14.8.
Found: C, 44.7; H, 3.2; N, 14.8.

The *dichloride IVa* was also prepared by treating the monohydrazide IIa, obtained from 5.5 g. of anhydride Ia, with 10.0 g. of phosphorus pentachloride in 60 ml. of phosphorus oxychloride and 50 ml. of benzene on the steam-bath for 15 minutes. The reaction mixture was filtered and worked up in the same manner as above to yield 1.5 g., 30%, IVa. A purified sample did not depress the m.p. of the dichloride IVa prepared above.

4,5-Trimethylenepyridazine (Va). *Procedure B.* A 3.00-g. (0.016 mole) sample of 3,6-dichloro-4,5-trimethylenepyridazine (IVa) was reduced by refluxing with 4.56 g. of red phosphorus and 32 ml. of freshly distilled, constant boiling hydriodic acid for 14 hrs.; 65 ml. of water then was added and the phosphorus was removed by filtration. The filtrate was evaporated *in vacuo* to a yellow oil which was taken up in cold water and neutralized with aqueous sodium hydroxide. This solution was extracted with chloroform, the extract was dried over sodium sulfate, and the chloroform was evaporated. Recrystallization of the residue from petroleum ether produced 1.36 g., 72% of Va in the form of colorless needles, m.p. 83–86°. Vacuum sublimation over an oil-bath maintained at 130° produced crystalline Va, m.p. 85–87°.

Anal. Calc'd for $C_7H_8N_2$: C, 70.0; H, 6.7; N, 23.3.

Found: C, 69.8; H, 6.5; N, 23.2.

4,5-Dihydro-3,4-trimethylenepyridaz-3(2)-one (VIIIa). *Procedure C.* Following a general technique 8.46 g. (0.05 mole) of ethyl-2-cyclopentanone acetate (VIIa) in 125 ml. of ethanol was refluxed for four hours with 2.50 g. (0.05 mole) of hydrazine hydrate and 5 ml. of acetic acid in 125 ml. of ethanol and was evaporated on the water-bath under reduced pressure. The residue was recrystallized directly from the reaction flask with 1:1 petroleum ether-benzene to produce 6.45 g. (93%) of VIIIa as white crystals, m.p. 130–133°.

3,4-Dimethylpyridaz-3(2)-one (IXb). *Procedure D.* Following a procedure given by Poppenberg (20), 18.93 g. (0.15 mole) of 4,5-dihydro-3,4-dimethylpyridaz-3(2)-one (VIIIb) was taken up in 50 ml. of warm acetic acid and 8 ml. (0.15 mole) of bromine was added slowly with stirring. The reaction mixture was cooled and the crystal mass was removed and dried to produce 27 g. (88%) of white crystalline 3,4-dimethylpyridaz-3(2)-one hydrobromide, which was recrystallized from acetic acid, m.p. 183–185°.

A 10.0-g. portion of this hydrobromide was taken up in 50 ml. of hot water and neutralized with concentrated aqueous sodium hydroxide, cooled, filtered, washed with 15 ml. of water, and the colorless crystals were dried. This produced 5.6 g. (93%) of 3,4-dimethylpyridaz-3(2)-one (IXb), m.p. 230–231°.

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SUMMARY

3,4- and 4,5-Dimethyl-, 3,4- and 4,5-trimethylene-, and 3,4- and 4,5-tetramethylene-pyridazine have been prepared.

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