Pyridazines. VII. Some 3-Dialkylaminopyridazines (1)

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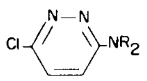
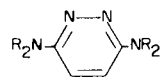
Pyridazines have become increasingly the subject of attention (*cf.* 3-5) during the course of the intermittent disclosure (1,6) of our work. A considerable range of biological effects has been reported (3-5) for these cyclic hydrazines which are the only diazines not found in Nature. Our investigations of 3,6-*bis*-(dialkylaminoalkoxy)pyridazines and their salts (7,8) led to uncovery of valuable levels of neuromuscular blocking among such series (9-11), and impelled us further to probe allied types for activity. The present contribution relates to the preparation of certain 6-chloro-3-dialkylaminopyridazines and their reactions with various amines (*cf.* 12, as also 3-5, 13-18), and basically-substituted alkoxides and mercaptides (*cf.* 7).

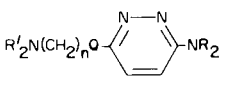
The mode of synthesis for the presently reported series of 3-dialkylaminopyridazines has followed that employed (7) for 3-(2-diethylaminopropylamino)-6-(3-diethylaminopropoxy)pyridazine. Here, the requisite secondary amine was caused to act upon 3,6-dichloropyridazine. Depending upon the severity of conditions imposed, either one halogen was replaced to form I, or with both halogens, giving II (*cf.* 12-18). The former was then used in reactions with the sodium (or, potassium) salts of basic alcohols or mercaptans to prepare target compounds of structure III. Further, by heating I with dialkylaminoalkylamine types, IV resulted. In some instances, the intermediate, I, was dehalogenated catalytically to form (*e.g.*) V. That transformation proved to be helpful in the removal of varying amounts of unchanged I from the products III or IV, since V could be fractionated from the mixtures with ease. Compounds of type III have been assembled in the Table.



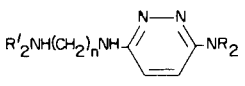
I



II

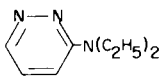


III



IV

Q = O or S; n = 2,3; R and R' = alkyl



V

EXPERIMENTAL (19)

Intermediates.

The requisite maleic hydrazides were converted into 3,6-dichloropyridazine and 3,6-dichloro-4-methylpyridazine by the action of phosphorus oxychloride (*cf.* 7).

Published procedures were used as basis for synthesis of the following alcohol types: 4-diethylaminobutanol (20,21); 5-diethylaminopentanol (*cf.* 22,23 for modification of ref. 24); 2-(2-diethylaminoethoxy)ethanol (25,26); and 1,3-*bis*-(diethylamino)-2-propanol (27). 4-Diethylaminobutyl mercaptan (28) and 1-benzylpiperazine (29) were also made by literature methods.

6-Chloro-3-dialkylaminopyridazines.

6-Chloro-3-dimethylaminopyridazine.

A mixture of 44.7 g. (0.3 mole) of 3,6-dichloropyridazine, 268 g. of 25% (w/v) aqueous dimethylamine solution, and 700 ml. of methanol containing 6 ml. of concentrated hydrochloric acid was placed in a pressure vessel and shaken at 120-130° for 24 hours. The resulting reddish liquid was concentrated *in vacuo*, and an excess of 50% sodium hydroxide solution added to the pasty residue. The product was extracted with methylene chloride, dried (sodium sulfate), and concentrated. Crystallization of the yellowish crystalline solid from hexane afforded 37.9 g. of pale straw colored plates, which melted to an opaque liquid at 78-79° (30). Analyses indicated presence of some 3,6-*bis*-(dimethylamino)-pyridazine; this was removed by formation of the hydrochloride in ethanol-pentane, then crystallizing that salt once from ethanol-pentane and once from propanol-2. An 85.5% recovery of pure hydrochloride was isolated as white blades, m.p. 230-231° dec.

Anal. Calcd. for $C_6H_8ClN_3 \cdot HCl$: N, 21.65; Cl (ionic), 18.27. Found: N, 21.60; Cl (ionic), 18.30.

6-Chloro-3-diethylaminopyridazine.

3,6-Dichloropyridazine and an excess of diethylamine were caused to react in methanol solution during 10 hours at 120-130° in a rocking autoclave. The resulting mixture was taken to dryness *in vacuo*, dissolved in ice water, basified with sodium hydroxide, and the product extracted with ether. The extracts were washed with saturated brine, dried, and fractionated to afford a 76% yield of 6-chloro-3-diethylaminopyridazine of b.p. 96-98° (0.1 mm.), which solidified to a yellowish crystalline mass, m.p. 46-68°. Two

Table

3-Diethylamino-6-dialkylaminoalkoxypyridazines

-OR	Base or Salt(a)	Appearance	B.p., °C(mm) [M.p., °C]	(Solvent)(b)	Yield, %	Formula	Analyses Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
$-O(CH_2)_2N(C_2H_5)_2$	B	Pale yell. oil	110-111 (0.1)	1.5162	79.5	$C_{14}H_{26}N_4O$	63.13	9.84	21.03	63.33	9.95	21.27
	2Mb	Creamy needles	[155.5-156.5]	(Pr-Eo)		$C_{16}H_{32}Br_2N_4O$	33.03(c)		12.28	33.30(c)		12.46
$-O(CH_2)_2N(C_2H_5)_2$	B	Pale yell. oil	*ca.* 140(9μ)	1.5137	61.6	$C_{15}H_{28}N_4O$	64.23	10.06	9.99(d)	64.33	9.74	9.93(d)
$-OCH[CH_2N(C_2H_5)_2]_2$	B	Golden oil	154-156 (0.08)	1.5058	80	$C_{19}H_{37}N_5O$	63.91	10.61	19.92	65.18	10.75	19.61
$-O(CH_2)_4N(C_2H_5)_2$	B	Yellow oil	*ca.* 170 (5μ)	1.5134	63	$C_{16}H_{30}N_4O$	65.27	10.27	19.03	65.57	10.39	17.98; 18.27
$-OCH(CH_2)_3N(C_2H_5)_2CH_3$	B	Golden oil	*ca.* 120 (3μ)	1.5078	67	$C_{17}H_{32}N_4O$	66.19	10.46	9.08(d)	66.12	10.48	8.89(d)
$-O(CH_2)_5N(C_2H_5)_2$	B	Straw col. oil	*ca.* 70 (2μ)	1.5085	67	$C_{17}H_{32}N_4O$			18.16	66.13	10.63	18.35
	2 Pic	Yellow needles	[121-122]	(E-Pe)		$C_{17}H_{32}N_4O\cdot 2C_6H_3N_3O_7$	45.43	5.00	10.96(e)	45.69	5.09	10.81
$-O(CH_2)_2O(CH_2)_2N(C_2H_5)_2$	B	Golden oil	*ca.*180 (4μ)	1.5092	49	$C_{16}H_{30}N_4O_2$	61.90	9.74	9.02(d)	61.90	9.62	8.96(d)

(a) B, base; Mb, methobromide; Pic, picrate. (b) E, ethanol; Eo, ether; Pe, pentane; Pr, propanol-1. (c) Bromine. (d) Basic nitrogen, by acetous-perchloric acid. (e) Nitro nitrogen, by titanium trichloride titration.

crystallizations from pentane gave the pure compound as straw-colored microcrystals, m.p. 49.5-50°. Subsequent to completion of this work, the compound has been reported to have m.p. 49-51° (30) and 50.5-53.5° (33).

Anal. Calcd. for $C_8H_{12}ClN_3$: Cl, 19.10; N, 22.63. Found: Cl, 19.00; N, 22.68.

6-Chloro-3-diethylaminopyridazine hydrochloride was formed in propanol-2, and crystallized from propanol-2 and ether. It was a cryptocrystalline white solid, m.p. 133.5-134.5°.

Anal. Calcd. for $C_8H_{12}ClN_3\cdot HCl$: N, 18.92; Cl (ionic), 15.96. Found: N, 18.77; Cl (ionic), 15.81.

6-Chloro-3-(di-*n*-butylamino) pyridazine.

A mixture of 14.9 g. (0.1 mole) of 3,6-dichloropyridazine with 28.5 g. (0.22 mole) of di-*n*-butylamine was stirred under reflux at 122-125° for 10 hours, then the brown oil was diluted with ether. The precipitated di-*n*-butylamine hydrochloride (14.2 g., 86%) was removed and the filtrates fractionated to give 22.8 g. (95.5% yield) of yellow oil, b.p. 145-153° (0.15-0.2 mm). It solidified to a waxy solid, m.p. 52-54°, which crystallized well from pentane as warty aggregates of yellowish needles, m.p. 55-56°. Combustion analyses indicated contamination, apparently by the *bis* compound, and that could not be removed by crystallization. It was subjected to chromatography on alumina with benzene-pentane (3:7) as eluant, then crystallized from pentane to obtain the pure compound as bundles of white needles, m.p. 57-57.5°. The pure 6-chloro-3-(di-*n*-butylamino)pyridazine showed marked electrostatic charge. A more readily purified product resulted from reaction of the components in refluxing ethanol in the presence of a catalytic amount of hydrochloric acid (*cf.* 7). Since completion of this work, several other modes for preparation of the compound have been reported (14,24,35) m.p. 57-58° (14,35).

Anal. Calcd. for $C_{12}H_{20}ClN_3$: Cl, 14.66; N, 17.37. Found: Cl, 14.84; N, 17.48.

3-Diethylamino-6-(diethylaminoalkoxy)pyridazines.

The series of 3-diethylamino-6-(diethylaminoalkoxy)pyridazines summarized in the Table were prepared in a uniform manner from 6-chloro-3-diethylaminopyridazine. An appropriate basic alcohol was converted to the alkoxide by reaction with sodium (or, potassium) in refluxing xylene under a nitrogen blanket. To that, there was added gradually a solution of the pyridazine derivative (1 equivalent) in warm xylene. At the completion of addition, the mixture was stirred and refluxed under nitrogen for 10 to 15 hours, cooled, and the product extracted with concentrated hydrochloric acid. The extracts were concentrated *in vacuo*, and the base liberated with sodium hydroxide. Either methylene chloride or ether was satisfactory for extraction of the base, which was then washed with saturated brine, dried (sodium sulfate), and fractionated. In certain instances, removal of unchanged 6-chloro-3-diethylaminopyridazine (usually some 0.5% to 3% of the compound was recovered even with 15% excess of potassium alkoxide) was extremely difficult by fractional distillation. When the rough distillate gave a positive Beilstein test, it was expedient to subject it to catalytic dehalogenation in ethanol at 3 atmospheres using 10% palladium-charcoal in the presence of sodium hydroxide. Thereafter, the desired pure bases could be isolated by fractional distillation, for 3-diethylaminopyridazine could be separated readily.

Other 3-Diethylaminopyridazines.

3-Diethylaminopyridazine.

6-Chloro-3-Diethylaminopyridazine was dehalogenated in ethanol solution at 25° in the presence of one equivalent of sodium

hydroxide, using a 10% palladium-charcoal catalyst, under 48 psi. of hydrogen. Uptake of hydrogen ceased after absorption of one equivalent. The desired base was isolated by fractionation of the filtered reaction mixture. An 86.5% yield of colorless oil was collected at 68-68.5° (0.03 mm.); n_D^{25} 1.5442. The same compound resulted as by product from purification of the 3-diethylamino-6-(diethylaminoalkoxy)pyridazines.

Anal. Calcd. for $C_8H_{13}N_3$: C, 63.54; H, 8.66; N, 27.79. C, 63.88; H, 8.67; N, 27.67.

3-Diethylamino-6-(4-diethylaminobutylmercapto)pyridazine.

Potassium 4-diethylaminobutylmercaptide was formed and then caused to react with 6-chloro-3-diethylaminopyridazine in xylene, under nitrogen, after the method described for the compounds in the Table. The usual method of isolation (v.s.) afforded the desired basic thioether in 62% yield. It was a yellow oil, b.p. *ca.* 136-140° (0.1 micron); n_D^{25} 1.5508.

Anal. Calcd. for $C_{16}H_{30}N_4S$: C, 61.89; H, 7.94; S, 10.33. Found: C, 62.19; H, 9.71; S, 10.30.

3-Diethylamino-6-(3-diethylaminopropylamino) pyridazine.

6-Chloro-3-diethylaminopyridazine (9.28 g., 0.05 mole) and 3-diethylaminopropylamine (15.63 g., 0.15 mole) were stirred well at 150-155° under nitrogen for 24 hours. The excess amine was removed by steam distillation, the residue concentrated *in vacuo* and then saturated with sodium chloride prior to rendering strongly basic with sodium hydroxide. The basic material was taken into ether, and the extracts washed well with saturated brine, dried, and fractionated. A fore-run of 1.94 g. of 6-chloro-3-diethylaminopyridazine was collected b.p. *ca.* 100° (0.1 mm.) and then 13.19 g. of golden oil, b.p. *ca.* 150° (3 microns). The latter was the desired compound, contaminated by starting material. It was purified by catalytic dehalogenation (v.s.), and repeated distillation. The pure 3-diethylamino-6-(3-diethylaminopropylamino)-pyridazine was collected as a bright yellow oil (6.72 g., 62% yield based upon non-recovered 3-chloro-6-diethylaminopyridazine), b.p. *ca.* 170° (5 microns); n_D^{25} 1.5387.

Anal. Calcd. for $C_{15}H_{29}N_5$: C, 64.47; H, 10.46; N (basic), 10.02. Found: C, 64.70; H, 10.60; N (basic), 9.96.

6-(4-Benzyl-1-piperazinyl)-3-diethylamino pyridazine.

3-Chloro-6-diethylamino pyridazine (9.29 g., 0.05 mole) and 1-benzylpiperazine (21.1 g., 0.12 mole) were stirred under nitrogen and heated at 120-130° for 10 hours. It was then basified strongly (sodium hydroxide) and steam distilled. The residual mixture was extracted well with ether, washed with saturated brine, dried, and fractionated. Two distillations of the main fraction gave 10.96 g. (67.5% yield) of product as a golden oil b.p. *ca.* 200° (0.3 micron), n_D^{25} 1.5913.

Anal. Calcd. for $C_{19}H_{27}N_5$: C, 70.12; H, 8.36; N, 21.52. Found: C, 70.17; H, 8.13; N, 21.86.

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