vacuum distillations, 3.7 g. (39%) of a pale yellow liquid, b.p. 135–136° (1 mm.), was obtained, $n^{25}D$ 1.6308.

Anal. Calcd. for $C_{11}H_{10}OS$: C, 69.5; H, 5.3; S, 16.8. Found: C, 69.6; H, 5.5; S, 16.0.

Intractable tars resulted when compound I was treated with diazomethane solution. Etherification procedures wherein the lithium salt of I was treated with methyl iodide or dimethyl sulfate, or where the sodium salt was treated with methyl iodide, were unsuccessful.

The Reaction of Sulfur with Phenylbutene.—(a) To 500 g. of stirred molten sulfur was added dropwise 63 g. of 1-phenyl-1-butene, b.p. 67–69° (5 mm.).[31] The reaction vessel was maintained at a pressure of 270–330 mm., and 56 g. of an orange distillate was collected. Fractionation of this product yielded 39 g. of unreacted olefin, b.p. 45–48° (2 mm.); 1.75 g. of material of b.p. 48–80° (2 mm.); and a dark brown residue. Recrystallization of the second fraction from 85% ethanol produced 1.24 g. (1.6%) of V as colorless needles, m.p. 35–38°. (b) A mixture of 101 g. of 1-phenyl-1-butene and 70.5 g. of sulfur was heated at 195–200° for 13 hours. By distillation, 9.9 g. of a fraction boiling at 80–120° (3 mm.) was secured along with 14.3 g. of recovered olefin, b.p. 96–98° (2 mm.), m.p. 36–38°.

Attempted Nitrosation of I.—(a) Addition of a solution of I and sodium nitrite in aqueous ethanol to cold, dilute hydrochloric acid produced VII and a trace of yellow solid, m.p. 196–198°. (b) Addition of a solution of I and sodium nitrite in aqueous base to cold hydrochloric acid gave a dark-colored base-insoluble solid. (c) Nitrogen oxides and I gave intractable oils and VII. (d) Isoamyl nitrite was dropped into a solution of I in ether through which hydrogen chloride was bubbling. VII and tars were isolated.

The Conversion of I to VII by Atmospheric Oxygen.—In each case 10 ml. of solvent was added to 100 mg. of I in a 25-ml. erlenmeyer flask which was then loosely stoppered with cotton. The solvents were reagent grade or were purified prior to use, except for petroleum ether (40–60°) which was a practical grade and chloroform which was U.S.P. and contained a small amount of alcohol. Observations were made after 0.25, 3.5 and 18 hours. The benzene, carbon tetrachloride, carbon disulfide and petroleum ether solutions were purple when made up and showed no further change on standing for 18 hours. The dioxane, ether and chloroform solutions had acquired a reddish tinge when observed at the end of 3.5 hours, and were redder at the end of 18 hours; no precipitation was observed, and almost all of I could be recovered as such. The solution in absolute ethanol had deposited a slight precipitate at 3.5 hours and the solute had completely precipitated as VII at 18 hours. The 95% ethanol and methanol solutions contained small precipitates at the end of 0.25 hour, and precipitation was complete at 18 hours. (In the three preceding cases, the supernatant liquid was colorless at 18 hours.) A heavy precipitate was deposited almost immediately from pyridine solutions. A carbon disulfide solution of I is markedly dichroic: red by reflected light, purple by transmitted light. VII crystallized from dioxane as dark green needles, m.p. 304–305°. VII dissolves in concentrated sulfuric acid to form a brilliant green solution; dilute or concentrated solutions of alkalies readily decompose VII.

Anal. Calcd. for $C_{20}H_{12}O_2S_2$: C, 69.0; H, 3.4; S, 18.4. Found: C, 68.5; H, 3.3; S, 18.4.

Solutions in morpholine or piperidine gradually deposit colorless crystals which are sulfur-free. The product from morpholine melts at 103–104° dec.

Anal. Found: C, 49.5; H, 8.0.

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CINCINNATI, OHIO

(31) J. Levy and M. Drobeitzka-Gombinska, *Bull. soc. chim.*, **49**, 1769 (1931).

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Pyridazine Derivatives. III.[1,2] Some 3,6-Disubstituted Pyridazines Having Neuromuscular Blocking Activity

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A series of pyridazines bearing basic substituents in positions 3 and 6, having the general structure I, was prepared for investigation as potential neuromuscular blocking agents. Several of the compounds reported, especially those having a three-carbon chain as A and A′ (in structure I), showed good potency with few side-effects.

Agents which selectively block neuromuscular transmission have found clinical use in conjunction with relatively light anesthesia during a variety of operations.[3] The pharmacology and chemistry of this group of drugs have been the subject of much investigation, as indicated in a number of reviews.[4–9] It has been shown that the activity of such compounds is closely associated with the presence of (at least) two quaternary groups situated about 15 Å. apart. There are two principal modes for depressing the activity of skeletal muscle; those producing competitive blocking resemble *d*-tubocurarine, and those which cause depolarization at the neuromuscular junction are similar to decamethonium salts. It was of interest to determine whether the bis-quaternary salts of certain 3,6-disubstituted pyridazines would have value as neuromuscular blocking agents without the side-effects resulting from lack of selectivity of action, as an influence on preganglionic autonomic transmission. A number of pyridazines having the general structure I was synthesized and salts (quaternary ammonium and acid-addition salts) prepared therefrom. Several representatives had high levels of neuromuscular blocking activity, with the

(1) Previous contribution: E. A. Steck, R. P. Brundage and L. T. Fletcher, THIS JOURNAL, **76**, 3225 (1954).

(2) Presented before the Medicinal Division of the American Chemical Society, Chicago, Ill., Sept., 1953.

(3) F. F. Foldes, T. S. Machaj, R. D. Hunt, P. G. McNall and P. C. Carberry, *J. Am. Med. Assoc.*, **150**, 1559 (1952).

(4) L. E. Craig, *Chem. Revs.*, **43**, 285 (1948).

(5) K. R. Unna, *et al.*, *Ann. N. Y. Acad. Sci.*, **54**, 297 (1951).

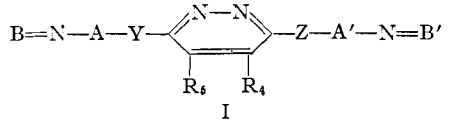
(6) D. B. Taylor, *Pharmacol. Revs.*, **3**, 412 (1951).

(7) W. D. M. Paton and E. J. Zaimis, *ibid.*, **4**, 219 (1952).

(8) L. O. Randall and L. M. Jampolsky, *Am. J. Physical Med.*, **32**, 102 (1953).

(9) W. Schneider, *Arzneimittel-Forschung*, **3**, 597 (1953).

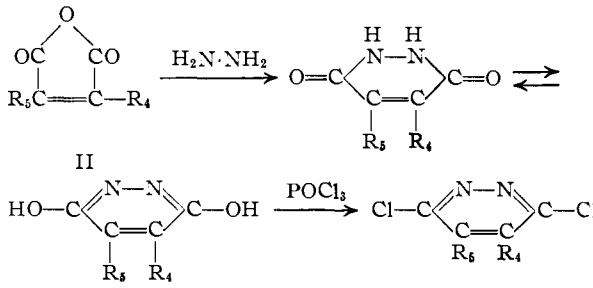
mode of action influenced considerably by the nature of the quaternizing group.[10] Details concerning the testing of the present series, and demonstration of satisfactory selectivity of blocking action will be reported elsewhere by Dr. J. O. Hoppe and associates.



I

B = N— and B′ = N— represent tertiary amino groups
A and A′ are lower alkylene (or oxygen-interrupted) radicals
Y represents O, S, or NH
Z represents O or S
R_4 and R_5 are hydrogen or lower-alkyl radicals

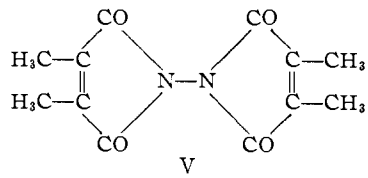
The pyridazine types were all prepared from maleic anhydrides II by the scheme outlined below, with the 3,6-dichloropyridazines IV as key intermediates. Preparation of maleic hydrazide (1,2-dihydropyridazine-3,6-dione (III)),[1,11–13] and the related 4-methyl type (citraconic hydrazide)[14,15,15a] has been reported in the literature. In the case of dimethylmaleic hydrazide (pyrocinchonic hydrazide), bis-(dimethylmaleic)-hydrazide (V) was obtained as a by-product. The interaction of the several maleic hydrazides III with phosphorus oxychloride gave the desired 3,6-dichloropyridazines (IV). 3,6-Dichloropyridazine and the related 4-methyl compound are known.[12,15a]



II

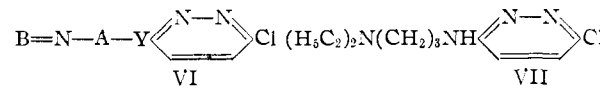
III

IV

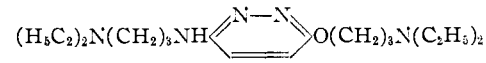


V

In the synthesis of the symmetrically substituted pyridazines (Table I), having Y = Z in structure I, the requisite 3,6-dichloropyridazine (IV) was caused to react with a tertiary-amino alcohol or mercaptan (in the form of its alkali metal derivative) in refluxing xylene. Certain of the reactions required use of the potassium salts of the alkanols for otherwise there was obtained both the symmetrical pyridazine and also the type in which only one halogen had entered into reaction, as VI. The series in which Y = NH in structure I (*e.g.*, VIII) was obtained by reaction of IV with 3-diethylaminopropylamine to produce VII, which was, in turn, caused to react with the sodium salt of a basic alkanol in xylene. A variety of salts, both acid addition and quaternary ammonium salts, was made from the several types of basically substituted pyridazines. Certain of the compounds were most conveniently obtained in a state of analytical purity by formation of the hydrochlorides or phosphates.



VI VII



VIII

As expected, the most pronounced pharmacological activity was found among the quaternary ammonium salts of the 3,6-disubstituted pyridazines. The neuromuscular blocking action was especially noteworthy in the cases where a three-carbon chain formed the spacing groups A and A′ in structure I. It may be noted that there is a degree of similarity between the pyridazine types here reported and certain aromatic types which have been found to have curaremimetic activity.[16,17]

Experimental[18,19]

A. 3,6-Dichloropyridazines

3,6-Dichloropyridazine was prepared by refluxing maleic hydrazide[11–13] with phosphorus oxychloride.[1,12,15a] The compound distilled at 89–91° (0.2 mm.) and was obtained in 82% yield; further purification by sublimation or recrystallization from hexane gave a product melting at 69–70°.

3,6-Dichloro-4-methylpyridazine.—Methyl maleic hydrazide[14,15,15a] was made from the anhydride (citraconic anhydride). To a solution of 26.0 g. (0.2 mole) of hydrazine sulfate in 30 cc. of water there was added 22.4 g. (0.2 mole) of methylmaleic anhydride, and the stirred mixture was refluxed for four hours. A partial take-off arrangement was used for the gradual concentration of the reaction mixture and to ensure completion of the reaction (*cf.* ref. 12). The mixture was finally diluted with 150 cc. of water, and the product was collected and dried, giving 19.0 g. of methylmaleic hydrazide. After two crystallizations of the crude material (m.p. 278–280°) from diethylene glycol monomethyl ether, a white microcrystalline solid was obtained; m.p. 285–287° dec. (reported[14,15] m.p. 277° and 289–290° dec.).

Anal. Calcd. for $C_5H_6N_2O_2$: C, 47.61; H, 4.80; N, 22.22. Found: C, 47.69; H, 4.70; N, 22.84.

A mixture of 360 g. (2.76 mole) of methylmaleic hydrazide and 2.4 liters of phosphorus oxychloride was refluxed with stirring for three hours. The excess phosphorus oxychloride was removed *in vacuo* and the residue hydrolyzed in ice-water, then rendered basic with ammonium hydroxide. The crude dichloro compound was collected and dried (424.0 g.), then distilled at 110–112° (1 mm.) to give 387.1 g. of 3,6-dichloro-4-methylpyridazine, m.p. 86–88°. Recrystallization of the compound from water gave a sample melting at 87–88°.

(10) L. O. Randall, *J. Pharmacol. Exptl. Therap.*, **105**, 16 (1952).
(11) T. Curtius and H. A. Foersterling, *J. prakt. Chem.*, [2] **51**, 391 (1895).
(12) R. H. Mizzoni and P. E. Spoerri, THIS JOURNAL, **73**, 1873 (1951).
(13) W. D. Harris and D. L. Schoene, U.S. Patent 2,575,954.
(14) M. Freri, *Gazz. chim. ital.*, **66**, 23 (1936).
(15) D. Stefanye and W. L. Howard, *J. Org. Chem.*, **19**, 117 (1954).
(a) At the time of this compilation this compound was just reported by J. Druey, K. Meier and K. Eichenberger, *Helv. Chim. Acta*, **37**, 121 (1954).
(16) C. A. Winter and J. T. Lehman, *J. Pharmacol. Exptl. Ther.*, **100**, 489 (1950).
(17) F. Häfliger and E. Girod, U. S. Patent 2,659,756.
(18) All analyses were performed under the direction of Mr. M. E. Auerbach and Mr. K. D. Fleischer in the Analytical Laboratories of this Institute.
(19) Unless stated otherwise, all melting points are corrected values, whereas boiling points are uncorrected.

TABLE I: 3,6-BIS-(DIALKYLAMINOALKOXY)- AND (DIALKYLAMINOALKYLTHIO)-PYRIDAZINES[a]

B = N	A	Y	R_4	R_5	Base[b] or salt	Appearance	M.p., °C.[c] [B.p., °C. (mm.)]	Solvent[d] ($n^{25}D$)	Yield, %	Calcd. C	Calcd. H	Analyses, % Found N	Found C	Found H	Found N
$(H_3C)_2N$	$(CH_2)_2$	O	H	H	B	Yellow oil	[130–133 (0.4)]	(1.4982)	85	56.67	8.72	22.03	56.75	8.71	22.08
					I	Prismatic needles	241–242 d.	Me–E		47.16[e]		10.41	46.7[e]		10.38
$(H_5C_2)_2N$	$(CH_2)_2$	O	H	H	B	Yellow oil	[132–137 (0.2)]	(1.4906)	70.5	69.91	9.74	18.05	70.18	9.68	18.02
					I	Prismatic needles	229–229.5 d.	Me–E		36.38	6.10	9.43[f]	36.68	6.14	9.34[f]
					P	Yellow needles	158–158.5	D		43.76	4.72	18.23	43.91	4.49	18.54
$(H_5C_2)_2N$	$(CH_2)_2$	O	CH_3	H	B	Golden oil	[140 (3×10^{-3})]	(1.4911)	84	62.93	9.94	17.27	62.98	10.09	17.50
					M	Microcryst.	145 vague	Me–D		44.36	7.45	31.08[e]	44.51	7.33	30.98[e]
$(H_9C_4)_2N$	$(CH_2)_2$	O	H	H	B	Yellow oil	[192–195 (0.1)]	(1.4853)	81	68.20	10.97	13.26	67.90	11.25	13.09
					N	Needles	149.5–150.5	A–E		52.53	8.45	15.32	52.50	8.76	15.45
C_8H_4ON[g]	$(CH_2)_2$	O	H	H	B	Blades	85.5–86	H–CH	68			16.56			16.79
$(H_3C)_2N$	$(CH_2)_3$	O	H	H	B	Prismatic needles	37.5–38	E	61	59.54	9.28	14.88[h,i]	59.96	8.87	14.44[h,i]
					C	Blades	222–223	D		47.32	7.91	19.96	47.14	7.68	20.24[e]
					M	Needles	240–241	Me–D		33.84[e]		8.90[h,i]	33.54[e]		8.90[h,i]
					Nb	Prisms	190–192	Me–D		47.07	5.36	22.37[e]	47.26	5.03	22.20[e]
$(H_3C)_2N$	$(CH_2)_3$	$O(CH_2)_3C(CH_3)H$			B	Pale yellow oil	[114–116 (5×10^{-4})]	(1.4972)	73	60.78	9.52	14.19[h,i]	60.49	9.22	13.65[h,i]
					Ph	Microcryst.	155–156.5	Me		49.81[j]		9.49	50.0[j]		9.56
					Nb	Blades	191–192	Me–A		47.81	5.54	21.94[e]	47.46	5.42	21.60[e]
$(H_3C)_2N$	$(CH_2)_3$	O	CH_3	CH_3	B	Pale yellow oil	[120–122 (5×10^{-4})]	(1.4970)	66	61.90	9.74	13.54[h,i]	61.60	9.22	13.07[h,i]
					C	Felted needles	250.5–251.5	Me–D		50.12	8.42	18.50[e]	50.18	8.45	18.42[e]
					Nb	Warty aggregates	207–208 d.	Me–A		48.52	5.70	21.53[e]	48.62	5.59	21.80[e]
$(H_5C_2)_2N$	$(CH_2)_3$	O	H	H	B	Yellowish oil	[130–132 (0.02)]	(1.4888)	70.5	63.87	10.13	16.56	64.15	10.32	16.98
					I	Prisms	186–187	A–E		40.78[e]		9.00	40.3[e]		9.48
					Nb/2	Microcryst.	181–182	*i*-Pr–E		14.30[e]		12.63	13.95[e]		12.99
$(H_5C_2)_2N$	$(CH_2)_3$	O	CH_3	H	B	Amber oil	[129–132 (0.01)]	(1.4981)	80	64.73	10.29	15.89	64.99	10.19	15.77
					Nb	Pale yell. plates	187–189 d.	Me–D–E		20.37[e]		10.71	20.18[e]		10.39
$(H_3C)_2N$	$CH_2C(CH_3)H$	O	H	H	B	Pale yell. oil	[84–89 (10^{-3})]	(1.4879)	84	59.54	9.28	19.84[k]	59.66	9.28	20.03
					I	Needles	198.5–200.5 d.	Me–D		44.8[e]		7.42[h,i]	44.4[e]		7.25[h,i]
$(H_5C_2)_2N$	$(CH_2)_4$	O	H	H	B[l,m]	Yellow oil	[*ca.* 125 (10^{-3})]	(1.4972)	63			15.29			15.58
$(H_5C_2)_2N$	$(CH_2)_3C(CH_3)H$	O	H	H	B[m,n]	Golden oil	[130–136 (10^{-3})]	(1.4870)	73	66.96	10.73	14.20	67.17	10.64	14.60
$(H_5C_2)_2N$	$(CH_2)_5$	O	H	H	B[l,m]	Yellow oil	[145 (2×10^{-4})]	(1.4982)	34.5				66.56	10.10	13.86
$(H_5C_2)_2N$	$(CH_2)_2O-(CH_2)_2$	O	H	H	B[l]	Yellow oil	[175 (3×10^{-3})]	(1.4890)	19.5	60.27	9.62	14.06	60.60	9.22	13.74
$(H_5C_2)_2N$	$(CH_2)_2$	S	H	H	B	Blades	52–53	Pe	69.5	56.10	8.83	16.36[o]	56.16	8.80	16.08
					M	Microcryst.	200–201 d.	*i*-Pr–A		30.02[e]		10.52	29.52[e]		10.65
$(H_5C_2)_2N$	$(CH_2)_3$	S	H	H	B	Amber oil	[140 (3×10^{-3})]	(1.5486)	71	58.33	9.25	15.12	58.49	9.53	15.10
					M	Yell. microcryst	184–184.5	A–E		28.52[e]		9.99	28.02[e]		10.20
$(H_5C_2)_2N$	$(CH_2)_4$	S	CH_3	H	B[m]	Yellow oil	[175 (10^{-3})]	(1.5493)	76	61.12	9.75	15.54[p]	61.12	9.45	15.23[p]
					O	Yellow needles	181–183 d.	Me		10.82[p]		4.72[h]	10.99[p]		4.79[h]

[a] Structure I in text, with Y = Z = O or S. [b] Legend: B, base; C, dihydrochloride; I, bis-(methiodide); M, bis-(methobromide); N, dinitrate; Nb, bis-(4-nitrobenzyl bromide); Nb/2, mono-(4-nitrobenzylbromide); O, dioxalate; P, dipicrate; Ph, triphosphate. Sodium salts of the basic alkanols (or thiols) were used unless stated otherwise. [c] d. signifies decomposition. [d] Legend: A, ethanol; CH, cyclohexane; D, acetone; E, diethyl ether; H, hexane; iPr, 2-propanol; Me, methanol; Pe, pentane. [e] Halogen. [f] *Anal.* Calcd. for $C_{18}H_{36}I_2N_4O_2$: I, 42.71. Found: I, 42.60. [g] Morpholinyl. [h] Basic nitrogen. Method was that developed by G. Toennies and T. P. Callan, *J. Biol. Chem.*, 125, 259 (1938). [i] Three of the four nitrogens present were found in this determination. [j] Phosphoric acid. [k] Also analyzed for basic nitrogen[h] by way of comparison with 3,6-bis-(3-dimethylaminopropoxy)-pyridazine (v.s.). Three nitrogens were titrable. *Anal.* Calcd. for $C_{14}H_{26}N_4O_2$: N_{basic}, 14.88. Found: N_{basic}, 14.38. [l] See Experimental for further details. [m] Potassium salt of basic alkanol (or thiol) was used. [n] Somewhat lower yields were obtained by use of the sodium derivative, but no other product could be isolated. [o] *Anal.* Calcd. for $C_{16}H_{30}N_4S_2$: S, 18.72. Found: S, 18.66. [p] Sulfur.

Anal. Calcd. for $C_5H_4Cl_2N_2$: C, 36.84; H, 2.47; Cl, 43.50; N, 17.19. Found: C, 36.95; H, 2.75; Cl, 43.6; N, 16.77.

3,6-Dichloro-4,5-dimethylpyridazine.—Dimethylmaleic hydrazide (pyrocinchonic hydrazide) was made from the corresponding anhydride (55.0 g., 0.435 mole) and hydrazine sulfate (56.5 g., 0.435 mole) in 150 cc. of water by refluxing for 3.5 hours as described above for the monomethyl type. Water (100 cc.) was added to the mixture, and the product crystallized from diethylene glycol monomethyl ether. The yield of dimethylmaleic hydrazide was 30.0 g.; it was obtained in the form of colorless needles, m.p. > 325°.

Anal. Calcd. for $C_6H_8N_2O_2$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.20; H, 6.06; N, 20.09.

The mother liquors from the recrystallization of dimethylmaleic hydrazide were diluted with water, and the resulting solid collected and dried. It was crystallized first from diethylene glycol monoethyl ether and then from diethylene glycol monomethyl ether to give 10.1 g. of bis-(dimethylmaleic)-hydrazide (V). The compound formed colorless needles, m.p. 238–240°.

Anal. Calcd. for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.29. Found: C, 57.86; H, 4.80; N, 11.56.

A mixture of 23.8 g. of dimethylmaleic hydrazide (0.17 mole) and 230 cc. of phosphorus oxychloride was refluxed with stirring for three hours and then the excess phosphorus oxychloride removed *in vacuo*. The residue was hydrolyzed in ice-water and rendered basic with ammonium hydroxide. The crude product weighed 28.5 g. when dry, and was sublimed at 120–140° (0.3 mm.) before crystallization from methanol; pure 3,6-dichloro-4,5-dimethylpyridazine was obtained as colorless needles, m.p. 120–121°.

Anal. Calcd. for $C_6H_6Cl_2N_2$: C, 40.70; H, 3.42; N, 15.83. Found: C, 40.63; H, 3.44; N, 15.88.

B. Dialkylaminoalkanols and Related Thiols

The following basic alcohols were obtained from commercial sources: 2-dimethylaminoethanol, 2-diethylaminoethanol, 2-dibutylaminoethanol, 2-(4-morpholino)-ethanol, 2-dimethylaminopropanol, 3-diethylaminopropanol and 4-diethylamino-1-methylbutanol. 3-Dimethylaminopropanol,[20] 4-diethylaminobutanol,[21] 5-diethylaminopentanol,[22] 2-diethylaminoethanethiol,[23] 3-diethylaminopropanethiol[23] and 4-diethylaminobutanethiol[23] were made by methods described in the literature.

C. 3,6-Bis-(dialkylaminoalkoxy)- and (dialkylaminoalkylthio)-pyridazines

The symmetrically substituted pyridazines shown in Table I are based upon the general structure shown as (I) with Y = Z. In general, these compounds were formed by the reaction of the appropriate 3,6-dichloropyridazine with two equivalents of the sodium (or potassium) derivative of the basic alkanol or alkanethiol in refluxing xylol. At the end of the reaction period of 12 to 15 hours, the mixture was filtered through Filter-Cel. The product was either isolated by direct fractionation of the filtrates, or by extraction of the base into concentrated hydrochloric acid with subsequent liberation, extraction (methylene chloride), drying, and fractionation. The salts were prepared in the usual manner. Only a few reactions deserve special attention.

3,6-Bis-(4-diethylaminobutoxy)-pyridazine and 3-Chloro-6-(4-diethylaminobutoxy)-pyridazine.—The reaction of 3,6-dichloropyridazine with two equivalents of sodium 4-diethylaminobutoxide in xylene was carried out in the usual manner. Two products were isolated, corresponding to the stepwise replacement of the chloro groups. 3-Chloro-6-(4-diethylaminobutyloxy)-pyridazine was obtained in 19% yield as an amber oil, b.p. *ca.* 110° (1.50 × 10^{-3} mm.); $n^{25}D$ 1.5097. It gave a white microcrystalline methobromide (from ethanol–ether), m.p. 174–174.5°.

Anal. Calcd. for $C_{13}H_{23}BrClN_3O$: N, 11.91; Br^-, 22.66. Found: N, 11.80; Br^-, 22.72.

3,6-Bis-(4-diethylaminobutoxy)-pyridazine was obtained together with 3-chloro-6-(4-diethylaminobutoxy)-pyridazine by use of sodium 4-diethylaminobutoxide, but only in 2.8% yield. It was more desirable to use potassium 4-diethylaminobutoxide (see Table I).

3,6-Bis-(5-diethylaminopentoxy)-pyridazine and 3-Chloro-6-(5-diethylaminopentoxy)-pyridazine.—3,6-Dichloropyridazine was interacted with potassium 5-diethylaminopentoxide in xylene; two compounds were formed. In addition to 3,6-bis-(5-diethylaminopentoxy)-pyridazine (obtained in 34.5% yield—see Table I), 3-chloro-6-(5-diethylaminopentoxy)-pyridazine was also produced (17% yield). The latter compound was a yellow oil, b.p. *ca.* 145° (2 × 10^{-3} mm.), $n^{25}D$ 1.4982.

Anal. Calcd. for $C_{13}H_{22}ClN_3O$: N (basic), 5.15. Found: N (basic), 4.92.

3,6-Bis-[2-(2′-diethylaminoethoxy)-ethoxy]-pyridazine and 3-Chloro-6-[2-(2′-diethylaminoethoxy)-ethoxy]-pyridazine.—The reaction of 3,6-dichloropyridazine with sodium 2-(2′-diethylaminoethoxy) ethoxide was run in the usual manner; two compounds were produced. The bis-substituted type (see Table I) was the minor product, being obtained in 19.5% yield. 3-Chloro-6-[2-(2′-diethylaminoethoxy)-ethoxy]-pyridazine was isolated in 38% yield; it was a golden oil, b.p. *ca.* 135° (3 × 10^{-3} mm.); $n^{25}D$ 1.5042.

Anal. Calcd. for $C_{12}H_{20}ClN_3O_2$: Cl, 12.95. Found: Cl, 12.77.

This base gave a monoöxalate which crystallized from ethanol–pentane as white microcrystals, m.p. 91.5–92.5°.

Anal. Calcd. for $C_{12}H_{20}ClN_3O_2 \cdot H_2C_2O_4$: N, 11.55; $H_2C_2O_4$, 24.75. Found: N, 11.56; $H_2C_2O_4$, 25.10.

D. 3-Dialkylaminopropylamino-6-dialkylaminoalkoxy-pyridazines

6-(3-Diethylaminopropylamino)-3-(3-diethylaminopropoxy)-pyridazine.—This base was prepared from 3,6-dichloropyridazine *via* 3-chloro-6-(3-diethylaminopropylamino)-pyridazine.

3,6-Dichloropyridazine (14.9 g., 0.1 mole) was dissolved in 30 cc. of acetone and to the solution was added a mixture of 39.2 g. (0.3 mole) of 3-diethylaminopropylamine, 50 cc. of water and 2 cc. of concd. hydrochloric acid. The stirred reaction mixture was refluxed for 24 hours, then excess hydrochloric acid added before removal of the solvents *in vacuo*. The residue was basified with 35% sodium hydroxide and extracted with methylene chloride, then the solvent distilled. To remove excess amine, the residue was steam distilled and the residue was extracted with methylene chloride and dried (sodium sulfate). Fractionation gave an 88.5% yield of 3-chloro-6-(3-diethylaminopropylamino)-pyridazine; b.p. *ca.* 130° (2 × 10^{-3} mm.). The distillate was crystallized from hexane to give the pure compound as colorless blades, m.p. 87–87.5°.

Anal. Calcd. for $C_{11}H_{19}ClN_4$: Cl, 14.61; N, 23.08. Found: Cl, 14.89; N, 23.32.

The 3-chloro-6-(3-diethylaminopropylamino)-pyridazine formed a dihydrochloride which separated from ethanol–ether as colorless microcrystals, m.p. 223–224°.

Anal. Calcd. for $C_{11}H_{19}ClN_4 \cdot 2HCl$: Cl, 22.46; N, 17.75. Found: Cl, 22.51; N, 17.60.

The reaction of 3-chloro-6-(3-diethylaminopropylamino)-pyridazine with one equivalent of sodium 3-diethylaminopropoxide was run in xylene with refluxing for 10 hours. Isolation of the base was accomplished as described in (B), giving a 40.5% yield of 6-(3-diethylaminopropylamino)-3-(3-diethylaminopropoxy)-pyridazine as a viscous, yellow oil; b.p. *ca.* 175° (3 × 10^{-3} mm.), $n^{25}D$ 1.5118.

Anal. Calcd. for $C_{18}H_{35}N_5O$: C, 64.05; H, 10.45; N, 20.75. Found: C, 64.0; H, 10.28; N, 20.74.

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(20) L. P. Kyrides, THIS JOURNAL, **72**, 745 (1950).

(21) E. Sarvasi, *Bull. soc. chim.*, 648 (1949).

(22) N. L. Drake, J. Van Hook, J. A. Garman, R. Hayes, R. Johnson, G. W. Kelly, S. Melamed and R. M. Peck, THIS JOURNAL, **68**, 1530, (1946).

(23) R. O. Clinton, U. J. Salvador, S. C. Laskowski and C. M. Suter *ibid.*, **70**, 950 (1948).