ml. of dry ether was added 24 mg. of magnesium powder. Then 162 mg. of propionyl chloride in 1 ml. of dry ether was added. The mixture was heated on the water bath for a few seconds and then set aside at room temperature for 1 hr. It was then diluted with 20 ml. of dry ether, refluxed for 30 min., set aside again at room temperature for 1 hr., and then treated with ice-cooled sodium carbonate solution to alkalinity. This mixture was extracted with ether; the ether solution was dried and then the ether was evaporated. The residue was 411 mg. of a yellow oil. This was chromatographed through a column of Florisil. After initial extractions with carbon tetrachloride, benzene, and methylene chloride, the column was extracted with ether. This latter fraction was then distilled in a Kugelrohr *in vacuo*, b.p. 205° (0.2 mm.). The infrared spectrum showed characteristic bands at 3.6, 5.88, 6.4, 7.0, 7.38, 9.6, and 14.2 μ.

Anal. Calcd. for $C_{23}H_{32}N_2O_3$: C, 71.84; H, 8.39. Found: C, 71.60; H, 8.68.

Acknowledgment.—The authors are indebted to Merck and Co., Inc., for a grant in support of this research project.

Synthesis and Pharmacological Study of Pyridazines. I. Alkoxypyridazines[1]

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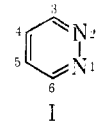
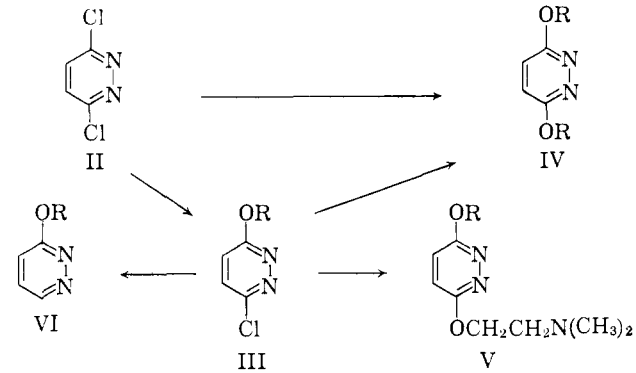
The chemistry of pyridazine (I), though related to pyrimidine, differs sharply in chemical reactivity due to the extreme polar nature of the molecule.[3] The positive nature of C-3 and -6 caused by the adjacent ring nitrogens is demonstrated not only by the ease of nucleophilic substitution at the ring carbons but also by the deshielding effects on the 3 and 6 hydrogen atoms as shown in the n.m.r. spectrum.[3] Because of the similarity of pyridine and pyrimidine, interest in the synthesis and pharmacological study of pyridazine derivatives



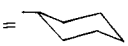
I

as potential medicinal agents has increased markedly in recent years. The pharmacology of many pyridazine derivatives has been studied,[4] including some with regard to CNS activities. A series of alkoxypyridazines, dialkylaminoalkoxypyridazines, and pyridazines containing both alkoxy and dialkylaminoalkoxy substituents was prepared for the purpose of investigating the structure–activity relationships and of evaluating the action on the central nervous system (Tables I–III).

The usual method of producing a 3-alkoxy-6-chloropyridazine has involved the treatment of 3,6-dichloropyridazine (II) with an equivalent amount of sodium alkoxide. We have shown using g.l.c. analysis that the product is invariably contaminated with II and IV. It was found that 3-alkoxy-6-chloropyridazines could be prepared best by heating for longer periods at greatly reduced temperatures.



II IV VI III V

a, R = CH_3
b, R = n-C_3H_7
c, R = i-C_3H_7
d, R = n-C_4H_9
e, R = n-C_5H_{11}
f, R = i-C_5H_{11}
g, R = 
h, R = $CH_2CH_2N(CH_3)_2$

The 3,6-bisalkoxypyridazines (IV) were prepared from II by treatment with excess sodium alkoxide or by treatment of III with excess sodium alkoxide using a higher temperature. Care had to be taken in preparing 3,6-bis(2-dimethylaminoethoxy)pyridazine (IVh) for it was found that 2-dimethylaminoethanol reacts violently with II on warming, producing copious volumes of smoke.

The 3,6-dialkoxypyridazines (nonbis) were prepared by adding a second mole of the new alkoxide at an appropriate temperature. Special problems were encountered in the process due to a side reaction involving alkoxide exchange, a phenomenon first observed in pyridazines by Coad, *et al.*[5] Conditions were sought to minimize the production of the two different bisalkoxy compounds which would be produced by means of alkoxide exchange. Variables such as the order of entry of the alkoxy groups, the temperature (which had to be sufficiently high to cause halogen displacement but

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(3) P. Coad, R. Coad, and C. Wilkins, *J. Phys. Chem.*, **67**, 2815 (1963).

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(5) P. Coad, R. A. Coad, and J. Hyepock, *J. Org. Chem.*, **29**, 1751 (1964).

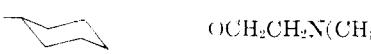
TABLE I

HALOPYRIDAZINES PREPARED AS INTERMEDIATES

Compd.	3-	6-	% yield	M.p., °C. Found	M.p., °C. Lit.	B.p., °C. (mm.)
II	Cl	Cl	70	66–67	66–67[3]	113–114 (8)
IIIa	Cl	OCH_3	74	90–91	90[4b]	174–175 (3)
IIIb	Cl	O-*n*-C_3H_7	87	66–67	65–66[7]	124–125 (9)
IIId	Cl	O-*n*-C_4H_9	85	47–48	48[4b]	148–150 (17)
IIIg	Cl		77	108–110	108–110[6]	153–154 (4)
IIIh	Cl	$OCH_2CH_2N(CH_3)_2$	60	46–47	46–47[5]	130–131 (2)

TABLE II

SYNTHETIC AND PHARMACOLOGICAL DATA OF PYRIDAZINES

Compd.	3-	6-	% yield	M.p., °C. Found	M.p., °C. Lit.	B.p., °C. (mm.) Found	B.p., °C. (mm.) Lit.	Dose,[a]
I	H	H	81			89–89.5	89–89.5[3] (14)	No effect up to 200
IIIc	O-*i*-C_3H_7	Cl	70	82–84	83–84[3]	129–131 (24)		125
IIIe	O-*i*-C_5H_{11}	Cl	85	58–60	58–59.5[7]	123–124 (3)		145
IVc	O-*i*-C_3H_7	O-*i*-C_3H_7	84	26–28	25–28[4b]	112–113 (4)	120–122 (11)[4b]	82
IVd	O-*n*-C_4H_9	O-*n*-C_4H_9	87	11–12		155–156 (8)	163–166 (11)[4b]	69
IVh	$OCH_2CH_2N(CH_3)_2$	$OCH_2CH_2N(CH_3)_2$	75	30–31		162–165 (4)	130–133 (0.4)[4b]	133
Va	OCH_3	$OCH_2CH_2N(CH_3)_2$	68			120–123 (4)	120–123 (4)[5]	83
Vc	O-*i*-C_3H_7	$OCH_2CH_2N(CH_3)_2$	77			140–141 (8)	131–132 (3)[5]	100
Vd	O-*n*-C_4H_9	$OCH_2CH_2N(CH_3)_2$	75			138–140 (4)	135–137 (3)[5]	59
Vg		$OCH_2CH_2N(CH_3)_2$	78	39–41	39–41[5]	178–185 (7)		56
VIc	O-*i*-C_3H_7	H	84			76–77 (4)	96–101 (12)[5]	145

[a] Dose required for 50% reduction in spontaneous activity.

TABLE III

ANALYTICAL, SYNTHETIC, AND PHARMACOLOGICAL DATA OF PYRIDAZINES

Compd.	3-	6-	% yield	M.p., °C.	B.p., °C. (mm.)	λ_{max}^{EtOH}, mμ	ε	Formula	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	N, % Calcd.	N, % Found	Dose,[a] mg./kg.
IVf	O-*i*-C_5H_{11}	O-*i*-C_5H_{11}	82	36–36.5	160–161 (4)	287	2100	$C_{18}H_{32}NO$	66.66	66.81	9.52	9.32	11.10	11.32	100
Vb	O-*n*-C_4H_7	$OCH_2CH_2N(CH_3)_2$	65		162–164 (8)			$C_{10}H_{19}N_3O_2$	58.64	58.30	8.50	8.29	18.65	18.44	77
Ve	O-*i*-C_5H_{11}	$OCH_2CH_2N(CH_3)_2$	60		132–135 (2)			$C_{13}H_{25}N_3O_2$	61.63	61.54	9.15	9.01	16.59	16.50	64
Vf	O-*i*-C_5H_{11}	$OCH_2CH_2N(CH_3)_2$	70	16–17	120–125 (2)	286	2100	$C_{13}H_{25}N_3O_2$	61.63	61.72	8.79	8.91	16.06	16.65	.
VIf	O-*i*-C_5H_{11}	H	83		93–94 (4)			$C_9H_{14}N_2O$	65.02	64.96	8.49	8.51	16.86	16.61	59
VIh	$OCH_2CH_2N(CH_3)_2$	H	78		137–138 (3)			$C_8H_{15}N_3O$	57.46	57.01	7.83	7.62	25.13	24.98	80

[a] Dose required for 50% reduction in spontaneous activity.

low enough to minimize exchange), and length of reaction were investigated. It is of interest to note that in all cases selected, it was possible to prepare pure nonbisdialkoxypyridazines.

The 3-alkoxypyridazines (VI) were prepared by hydrogenolysis of the corresponding 3-alkoxy-6-chloropyridazines.

The preliminary pharmacological evaluation of the derivatives included the gross observation of drug-induced effects in mice, and the measurement of spontaneous activity of mice as influenced by the derivatives. The compounds tested included pyridazine (I) and the derivatives IV–VI.

The gross behavior of male, Swiss Webster mice was studied for 2 hr. following the intraperitoneal injection of the compounds. The spontaneous activity was measured using photocell activity cages (Actophotometer, Metro Co.). Groups of five mice were injected intraperitoneally with varying doses of the test compounds. Fifty minutes after injection, the animals were placed in the activity cages and a 10-min. exploration period was allowed before the 15-min. test period was recorded. Each drug dose was injected into four groups of mice. The drug-induced activity was compared to the control activity of the mice injected with 0.9% NaCl solution. The per cent of control activity for dosage intervals of each drug was plotted, and the dose that produced a 50% reduction in activity was approximated.

Pyridazine (I) produced no noticeable effects on the gross or spontaneous activity in the doses tested (25–200 mg./kg.). The 3-alkoxy-6-chloropyridazine derivatives were not evaluated. The 3-alkoxy-6-(2-dimethylaminoethoxy)pyridazine derivatives in general showed an initial stimulation of activity followed by depression. The stimulation was of short duration, and only depression of activity was noted during the recording time of spontaneous activity. The doses (mg./kg.) producing a 50% reduction in spontaneous activity were: Va, 83; Vb, 77; Vc, 100; Vd, 59; Ve, 64; Vf, not tested; Vg, 56.

The 3,6-bisdialkoxypyridazine derivatives produced depression of activity. The doses (mg./kg.) producing

a 50% reduction in spontaneous activity were: IVc, 82; IVd, 69; IVf, 100; IVh, 133.

The 3-alkoxypyridazine derivatives all produced depression, except VIh which produced an initial stimulation followed by depression. The doses (mg./kg.) producing a 50% reduction in spontaneous activity were: VIc, 145; VIf, 59; VIh, 80.

Subsequent pharmacological studies being made include the rotarod technique to determine the degree of impairment of forced motor and coordinated activity, and the determination of the effects of experimental compounds on hexobarbital sleeping time and on pentylenetetrazol and strychnine convulsions in mice.

Experimental

3-Alkoxy-6-chloropyridazines (III).—Sodium (4.6 g., 0.2 g.-atom) was dispersed in 70 ml. of hot anhydrous xylene and the appropriate anhydrous alcohol (0.22 mole) was added over a period of 20 min. After all the sodium had reacted, a solution of 29.8 g. (0.20 mole) of 3,6-dichloropyridazine (II) prepared and purified by the method of Coad and Coad[6] in 50 ml. of anhydrous xylene was added over a period of 15 min. The internal temperature was kept below 60° by cooling during the addition. The mixture was heated at 60° for 10 hr., cooled to room temperature, and filtered. The xylene was removed *in vacuo*, and the residue was distilled through an efficient column.

The conditions were modified slightly for the preparation of IIIg. The internal temperature was raised to 95° during the last 6 hr. of heating. In the case of IIIh the xylene filtrates were washed with two 25-ml. portions of cold 30% NaOH solution and dried (Na_2SO_4) before distillation through the column. Certain of these compounds were reported previously[7] (see Table I).

3,6-Bisalkoxypyridazines (IV).—These could have been prepared directly from dichloropyridazine (II) with excess sodium alkoxide by traditional procedures described in the literature.[4b] In the particular cases in this series, the compounds were prepared by addition of a second mole of alkoxide for each mole of 3-alkoxy-6-chloropyridazine used. The temperature was raised to the boiling point of xylene for 3 hr. The mixture was cooled and filtered. The filtrate was concentrated *in vacuo*, dissolved in ethanol, hydrogenated in a Parr apparatus with ammonium hydroxide and activated 10% palladium on carbon, filtered, and concentrated *in vacuo*. The residue was distilled through an efficient column separating traces of pyridazine and monoalkoxypyridazine from the product. The yields ranged from 75–87%.

3-Alkoxy-6-(2-dimethylaminoethoxy)pyridazines (V).—Sodium (2.3 g., 0.10 g.-atom) was dispersed in 100 ml. of hot anhydrous xylene. To this was added 0.11 mole of the appropriate anhydrous alcohol. The mixture was stirred until the sodium disappeared and was heated to boiling. A solution consisting of 20 g. (0.10 mole) of IIIh and 50 ml. of anhydrous xylene was added over a period of 5 min. for lower alkoxides and 15 min. for higher ones. The reaction mixture was stirred and heated under reflux for 3 hr., cooled, and filtered. The filtrate was washed with 10 ml. of cold 30% NaOH solution and dried (Na_2SO_4). The xylene and excess alcohol were removed *in vacuo*. The purification of this crude product had to be varied for the different alkoxides. Compounds Va, Vd, Vf, and Vg were simply distilled through an efficient column. In the case of Vg, it was necessary to equip the side-arm condenser with a steam jacket since the product melts at 39–41°.

In the cases of Vb and Vc, the crude product was first freed from the halopyridazines which would interfere with the final distillation by hydrogenolysis in a Parr apparatus with 5 ml. of concentrated ammonium hydroxide, 2.0 g. of activated 10% palladium on carbon, and 100 ml. of ethanol. The ethanol was removed *in vacuo*, and the residue was washed with cold 10% NaOH solution and extracted with four 100-ml. portions of ether. The combined extracts were dried (Na_2SO_4), filtered through fresh sodium sulfate, and flash distilled to remove the solvent. The residue was then distilled through an efficient column.

(6) P. Coad and R. Coad, *J. Org. Chem.*, **28**, 1919 (1963).
(7) T. Itai and H. Igeta, *Yakugaku Zasshi*, **74**, 1195 (1954).

Hydrogenolysis of Halopyridazines.—The Parr hydrogenation apparatus was used in the hydrogenolysis of 3,6-dichloropyridazine to form pyridazine (I) which was purified by the method of Coad, *et al.*[3] It was also used for the preparation of 3-alkoxypyridazine (VIc, VIf, and VIh) by the hydrogenolysis of the appropriate 3-alkoxy-6-chloropyridazine (0.1 mole) using 50 ml. of ethanol, 10 ml. of concentrated ammonium hydroxide, and 5 g. of activated palladium on carbon at 3 atm. pressure. The mixture was filtered after cooling and the filtrate was slowly distilled. Absolute ethanol was added from time to time until a total of 800 ml. had been distilled and 80 ml. remained. The liquid was cooled, filtered, and distilled through an efficient column. The yields ranged from 78–84%.

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Novel Oral Hypoglycemic Agents. I. Hexahydroindeno[1,2-*c*]pyrroles and Indanamines[1]

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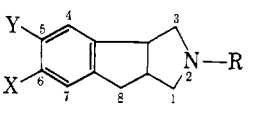
In a previous paper[3] the synthesis of some 1,2,3,3a,-8,8a-hexahydro-2-alkylindeno[1,2-*c*]pyrroles (I), a new class of heterocyclic compounds, was described, and their potential amoebicidal activity was investigated. Maximum *in vitro* amoebicidal activity of these compounds was $^1/_{32}$ that of emetine hydrochloride. To our surprise 1,2,3,3a,8,8a-hexahydro-2-butyl-5,6-dimethoxyindeno[1,2-*c*]pyrrole hydrochloride was found to possess high oral hypoglycemic activity in experimental animals. This observation led the authors to investigate systematically the oral hypoglycemic activity among other compounds of this class. It has been found that N-butyl compounds are the most active ones, though other alkyl substitutions also exhibit oral hypoglycemic activity. The results of the investigation are listed in Table I. From the table it appears that compounds **5**, **6**, **8**, and **11** are active.



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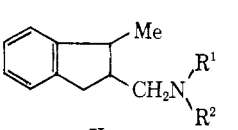

II

In order to ascertain whether the hexahydroindeno-[1,2-*c*]pyrrole structure is essential for the development of oral hypoglycemic activity, a few compounds of the type II have also been prepared. It has been found that two compounds of this class also possess appreci-

(1) This investigation was partly supported by the award of a scholarship to one of the authors (S. C. L.) by the Ministry of Education, Government of India.
(2) To whom inquiries regarding this paper should be sent.
(3) K. L. Pathak and B. Pathak, *J. Indian Chem. Soc.*, **38**, 253 (1961).