

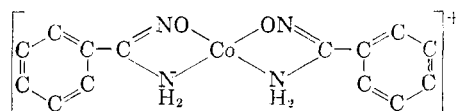
Fig. 2.—Continuous variations cobalt(II) and BAO at pH 12.5; curve 1, 573 m $\mu$ ; 2, 625 m $\mu$ ; 3, 550 m $\mu$ .

complex precluded a determination of the stoichiometry by this method.

In an attempt to stabilize the system, the blue complex was extracted into water-immiscible alcohols. Such an extraction is quite complete in a single volume of extractant. This increases the molar absorptivity of the complex by 50%.

Although all of the monoamidoximes, with the exception of 2-pyAO, form the blue complex, benzamidoxime gives a complex of greater stability and higher molar absorptivity. Continuous variation studies, Fig. 2, show that the complex exists in a two-to-one ratio of ligand to metal ion.

In order to assign a configuration to the blue species, it was necessary to determine if it were a charged complex. Investigations of this property were carried out in a Hittorf cell using tris-1,10-phenanthroline-iron(II) as a reference system. The results showed that the cobalt monoamidoxime complex was positively charged. From all of the data obtained, the blue cobalt benzamidoxime species, which exists in highly alkaline solutions, was assigned the formula



This structure necessitates cobalt being in the tervalent state. This is reasonable in view of the instability of the complex in the presence of reducing agents and the ultimate precipitation of cobaltic hydroxide out of strongly basic solutions.

The addition of alkali metal hydroxides to a solution containing cobalt and a diamidoxime such as oxamidoxime gives rise to a yellow complex. This species is not extractable into water-immiscible alcohols. The complex exhibits a greater stability toward chemical reducing agents than does the cobalt monoamidoxime complex.

**Acknowledgment.**—The authors wish to thank the Research Corporation for the financial assistance which made the majority of this work possible.

IOWA CITY, IOWA

[CONTRIBUTION NO. 483 FROM THE RESEARCH LABORATORIES OF HOFFMANN-LA ROCHE INC.]

## Piperidine Compounds. VII. The Synthesis of Arylpiperidinemethanol and Arylpiperidineethanol Compounds

BY JACOB FINKELSTEIN AND WARREN SOLODAR

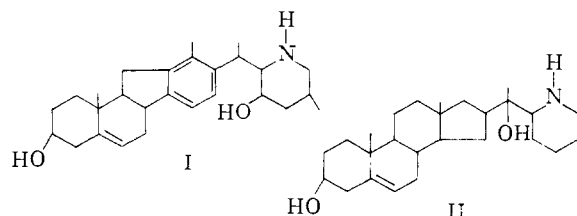
RECEIVED MARCH 28, 1959

A number of piperidine compounds of potential pharmacological interest was synthesized in a search for hypotensive activity based upon certain structural and biological relationships.

The tertiary veratrum alkaloids have various powerful pharmacological effects, particularly vaso-depressor properties,<sup>1</sup> and have been used as effective hypotensive agents in clinical trials.<sup>2</sup> The secondary veratrum bases also lower blood pressure and in addition have a specific anti-accelerator action on the heart and antagonize the effects of epinephrine on the heart.<sup>3</sup>

In a series of publications,<sup>4,5</sup> the structure of

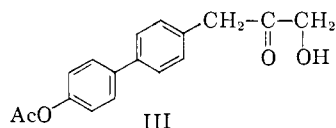
- (1) O. Kraymer and Acheson, *Physiol. Rev.*, **26**, 383 (1946).
- (2) E. D. Fries and J. R. Stanton, *Amer. Heart J.*, **36**, 725 (1948).
- (3) O. Kraymer, *J. Pharm. Exp. Therap.*, **96**, 422 (1949).
- (4) J. Fried, O. Wintersteiner, M. Moore, B. M. Iselin and A. Klingsburg, *THIS JOURNAL*, **73**, 2970 (1951).
- (5) C. Tamm and O. Wintersteiner, *ibid.*, **74**, 3842 (1952); O. Wintersteiner and N. Hosansky, *ibid.*, **74**, 4474 (1952).



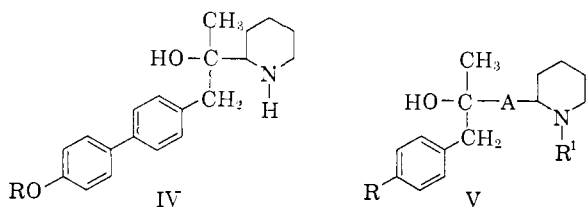
veratramine (I) was established as a steroid-like alkanolamine. However, on the basis of a formerly postulated structure, Uhle<sup>6</sup> prepared the synthetic steroid alkaloid II by treating 5-pregnene-3 $\beta$ -ol-20-one with 5-methyl-2-pyridyllithium and

- (6) F. C. Uhle, *ibid.*, **73**, 883 (1951).

reducing the resultant carbinol to the secondary amine. Despite the fundamental variation in chemical relationships, this product possessed a veratramine-like effect on the cardioaccelerator action of epinephrine at a comparable dose level. Linnel, *et al.*,<sup>7</sup> while investigating certain chemical structural and pharmacological relationships, found that the biphenyl compound III possessed marked desoxycorticosterone activity. This finding would appear to indicate that the biphenyl analog which

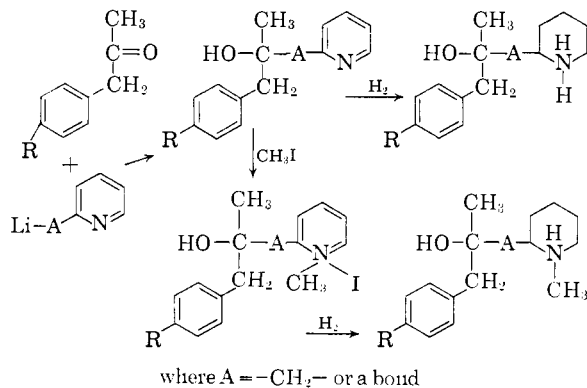


is spatially related to the steroid was capable of replacing the natural product. By combining the Uhle and Linnel approaches, it was of interest to synthesize compounds of the structure IV type for their pharmacological possibilities. To develop such hypotensive substances, the basic amine



and carbinol features were to be retained while the steroid would be replaced by the simpler yet structurally related groups. The program was extended further to synthesizing several series of compounds of the general formula V, as shown in Table I.

The chemical reactions involved in each series were similar. The required phenylacetone derivative was reacted with 2-pyridyllithium and 2-pyridylmethylithium. The resultant carbinols were reduced to their corresponding piperidines. Also, the pyridinecarbinols were quaternized with methyl iodide to be reduced to the N-methylpiperidinecarbinols, as



Series A, B, C and D are not described in the Experimental section, but the compounds are summarized in Table II. The 4-(4'-methoxyphenyl)phenylacetone required for series E and F was obtained by starting with *p*-

(7) W. H. Linnel, *et al.*, *Nature*, **167**, 237 (1951).

TABLE I

Series	R	A	R'
A	H	...	H and CH <sub>3</sub>
B	OCH <sub>3</sub>	...	H and CH <sub>3</sub>
C	H	-CH <sub>2</sub> -	H and CH <sub>3</sub>
D	OCH <sub>3</sub>	-CH <sub>2</sub> -	H and CH <sub>3</sub>
E	<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	...	H and CH <sub>3</sub>
F	<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	-CH <sub>2</sub> -	H and CH <sub>3</sub>

methoxybiphenyl.<sup>8</sup> This 4-(*p*-methoxyphenyl)phenyl methyl ketone was converted to the acetic acid derivative *via* the conditions of the Willgerodt reaction.<sup>9</sup> This acid was treated with thionyl chloride to form the acid chloride which reacted with ethyl ethoxymagnesium malonate<sup>10</sup> to eventually yield the acetone derivative.

**Acknowledgment.**—The authors are indebted to Dr. Al Steyermark and his associates for the microanalyses.

### Experimental

**4'-Methoxy-4-biphenylacetic Acid.**—A mixture of 48 g. of 4-(4'-methoxyphenyl)acetophenone<sup>8</sup> with 30 g. of morpholine and 10.2 g. of sulfur was refluxed for 15 hours. When cool, it was poured into 125 ml. of warm ethanol and a yellow crystalline compound was obtained. This thiomorpholide was filtered, dried and used without any further purification.

A suspension of 30 g. of the thiomorpholide in 200 cc. of 25% KOH was refluxed for 18 hours. The solution was acidified and the precipitated acid filtered. It was recrystallized from acetic acid to form a white crystalline substance, m.p. 182–184°, yield 25.4 g.

*Anal.* Calcd. for C<sub>15</sub>H<sub>14</sub>O<sub>3</sub>: C, 74.32; H, 5.82. Found: C, 74.60; H, 5.61.

**4'-Methoxy-4-biphenylacetyl Chloride.**—A mixture of 8 g. of the above acid and 10 cc. of freshly distilled thionyl chloride was warmed until the reaction became exothermic and continued for 2 hours. The excess thionyl chloride was removed *in vacuo* under nitrogen and the evaporation repeated twice with benzene. The acid chloride was thus obtained as a tan solid, m.p. 76–78°. It was used without further purification.

**4'-Methoxy-4-biphenyl-2-propanone.**<sup>10</sup>—In a 250-ml. 3-neck flask, 0.7 g. of magnesium turnings, 0.65 ml. of dry, ethanol and 2 drops of chloroform were warmed until the reaction started. Then, after adding 20 ml. of dry ether and gently refluxing, a solution of 4.35 g. of ethyl malonate and 2.6 ml. of dry ethanol in 3.3 cc. of ether was added and refluxing continued for 3.5 hours by warming until all the magnesium had reacted. Another 25 ml. of ether was added followed by the portionwise addition of the above acid chloride obtained from 8 g. of the acid as described. After stirring and refluxing for one hour, a dark immiscible oil separated. After cooling to room temperature, 1.8 ml. of concentrated sulfuric acid in 26 ml. of water was added. The aqueous phase was extracted well with ether which was evaporated to yield a solid residue. This product was then refluxed in a solution of 8 ml. of acetic acid, 1 ml. of sulfuric acid and 5.2 ml. of water until gas evolution had ceased. The solution was made alkaline with 10% sodium hydroxide and extracted with chloroform. The chloroform solution was clarified by filtration, dried and evaporated to dryness. The residue was triturated with benzene and filtered. The yellow solid, when recrystallized twice from Skellysolve B, became white, m.p. 79–82°. After purification by sublimation, the product melted at 82–84°, yield 5 g. (62.5%).

**$\alpha$ -(*p*-Methoxyphenyl)-benzyl- $\alpha$ -methyl-2-pyridine-methanol.**—To a solution of 2-pyridyllithium prepared as described by Wibaut<sup>11</sup> from 1.0 g. of freshly cut lithium pieces 8 ml. of *n*-butyl bromide and 8 g. of 2-bromopyridine at -45°, a solution of 13.5 g. of the ketone in 500 ml. of dry

(8) R. Fusco and L. Renieri, *C. A.*, **43**, 1034a (1949); *Gazz. chim. ital.*, **78**, 435 (1948).

(9) "Organic Reactions," Vol. 3, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 83.

(10) *Org. Syntheses*, **25**, 73 (1945).

(11) J. B. Wibaut, *Rec. trav. chim.*, **70**, 1054 (1951).

TABLE II

Series	No.	Compound	M.p., °C., or b.p. (mm.)	Formula	Calcd.			Found			Theoretical yield, %
					C	H	N	C	H	N	
A	1	$\alpha$ -Benzyl- $\alpha$ -methyl-2-pyridinemethanol	66-67 <sup>a</sup>	C <sub>14</sub> H <sub>15</sub> NO	78.80	7.09	6.57	79.05	7.26	6.29	43.4
	2	$\alpha$ -methyl-2-pyridinemethanol methiodide	148-149 <sup>b</sup>	C <sub>15</sub> H <sub>15</sub> NOI	50.70	5.10	3.94	50.93	4.71	3.99	52.5
	3	$\alpha$ -methyl-2-piperidinemethanol	95-97 <sup>c</sup>	C <sub>14</sub> H <sub>21</sub> NO	76.63	9.65	6.39	76.48	9.80	6.70	75.3
	4	$\alpha$ ,1-dimethyl-2-piperidinemethanol	119-120 (1)	C <sub>15</sub> H <sub>23</sub> NO	77.20	9.93	6.01	77.51	9.85	6.25	68.6
B	5	$\alpha$ - <i>p</i> -Methoxybenzyl- $\alpha$ -methyl-2-pyridine-methanol	130-131 (0.5)	C <sub>15</sub> H <sub>17</sub> NO <sub>2</sub>			5.76			5.74	45.2
	6	$\alpha$ -methyl-2-pyridinemethanol methiodide	156-157 <sup>d</sup>	C <sub>15</sub> H <sub>20</sub> NO <sub>2</sub> I	49.85	5.23	3.64	50.27	5.43	3.46	43.8
	7	$\alpha$ -methyl-2-piperidinemethanol	99-101 <sup>e</sup>	C <sub>15</sub> H <sub>21</sub> NO <sub>2</sub>	72.23	9.29	5.02	72.19	9.23	5.49	40.1
	8	$\alpha$ ,1-dimethyl-2-piperidinemethanol	132-133 (0.5)	C <sub>16</sub> H <sub>23</sub> NO <sub>2</sub>	72.94	9.57	5.32	73.07	9.63	5.20	57.0
C	9	$\alpha$ -Benzyl- $\alpha$ -methyl-2-pyridine-ethanol	132-134 (0.5)	C <sub>15</sub> H <sub>17</sub> NO	79.25	7.49	6.17	78.50	7.21	6.50	44.0
	10	$\alpha$ -methyl-2-pyridine-ethanol methiodide	162-164 <sup>f</sup>	C <sub>16</sub> H <sub>20</sub> NOI	52.00	5.46		52.07	5.43		66.2
	11	$\alpha$ -methyl-2-piperidine-ethanol	106-112 (0.5)	C <sub>15</sub> H <sub>21</sub> NO	77.25	9.87	6.01	77.53		6.07	58.8
	12	$\alpha$ ,1-dimethyl-2-piperidine-ethanol	123-125 (0.5)	C <sub>16</sub> H <sub>23</sub> NO	77.70	10.18	5.66	77.46	10.34	5.49	65.0
D	13	$\alpha$ - <i>p</i> -Methoxybenzyl- $\alpha$ -methyl-2-pyridine-ethanol	167-171 (0.5)	C <sub>16</sub> H <sub>19</sub> NO <sub>2</sub>	74.70	7.44	5.45	74.82	7.72	4.92	56.1
	14	$\alpha$ -methyl-2-pyridine-ethanol methiodide	118-120 <sup>g</sup>	C <sub>17</sub> H <sub>22</sub> NO <sub>2</sub> I	51.15	5.56	3.51	50.92	5.61	3.50	71.2
	15	$\alpha$ -methyl-2-piperidine-ethanol	117-119 <sup>h</sup>	C <sub>16</sub> H <sub>21</sub> NO <sub>2</sub>	72.96	9.57	5.32	72.66	9.51	5.25	42.1
	16	$\alpha$ ,1-dimethyl-2-piperidine-ethanol	144-146 (0.5)	C <sub>17</sub> H <sub>23</sub> NO <sub>2</sub>	73.60	9.82	5.05	73.27	9.88	4.84	65.7

<sup>a</sup> Colorless crystals from Skellysolve B. <sup>b</sup> From mixture of isopropyl alcohol and Skellysolve B. <sup>c</sup> White needles from Skellysolve B; hydrochloride, m.p. 218-221° from acetone-methanol. <sup>d</sup> Yellow product from isopropyl alcohol. <sup>e</sup> Colorless crystals from Skellysolve B. <sup>f</sup> From isopropyl alcohol. <sup>g</sup> From isopropyl alcohol. <sup>h</sup> From Skellysolve B.

ether was slowly added. The reaction mixture was stirred at -45 to -60° for 20 minutes and then permitted to warm up to 0°. After the addition of 60 ml. of water and 60 ml. of 4 N HCl, the first crop of the product was precipitated and filtered off. From the filtrate, the ether was separated, dried over anhydrous magnesium sulfate, evaporated and the residue crystallized from Skellysolve B to yield 7 g. of white crystals. This was recovered starting ketone, m.p. 80-84°.

The aqueous phase was freed from the volatile solvents by evaporation and a second crop was obtained which was combined with the first and dissolved in tetrahydrofuran and water. The free base was liberated by the addition of 4 N NaOH and then recovered by extraction with ether. The extract was dried, evaporated and the residue recrystallized from isopropyl alcohol-ligroin mixture. The compound was thus obtained as yellow crystals, m.p. 128-129°, yield 3.6 g.

*Anal.* Calcd. for C<sub>21</sub>H<sub>21</sub>NO<sub>2</sub>: C, 79.00; H, 6.63; N, 4.39. Found: C, 79.19; H, 6.85; N, 4.28.

The hydrochloride was obtained as yellow crystals by drying the original precipitate by azeotropic distillation with benzene and crystallizing it from alcohol-ether; m.p. 191-193°.

*Anal.* Calcd. for C<sub>21</sub>H<sub>22</sub>NO<sub>2</sub>Cl: C, 70.87; H, 6.23; N, 3.94. Found: C, 71.13; H, 6.30; N, 4.37.

$\alpha$ -[*p*-(*p*-Methoxyphenyl)-benzyl]- $\alpha$ -methyl-2-pyridine-methanol Methiodide.—A solution of 2 g. of the above carbinol was refluxed in 25 ml. of methanol with 1.5 ml. of methyl iodide for 6 days and then concentrated *in vacuo*. The oil residue was triturated with ether to form a solid. It was purified by recrystallization from acetone-Skellysolve; m.p. 160-164°, yield 76%.

*Anal.* Calcd. for C<sub>22</sub>H<sub>24</sub>NO<sub>2</sub>I·0.5H<sub>2</sub>O: C, 56.20; H, 5.32. Found: C, 56.47; H, 5.61.

$\alpha$ -[*p*-(*p*-Methoxyphenyl)-benzyl]- $\alpha$ ,1-dimethyl-2-piperidinemethanol.—A suspension of 4 g. of the above methiodide in 40 ml. of 95% ethanol was hydrogenated over 200 mg. of platinum oxide at room temperature and 300 lb. pressure. The reduced mixture was diluted with ethanol and warmed until the product dissolved before separating the catalyst by filtration. The cooled filtrate yielded the hydriodide as colorless crystals, m.p. 271-72°, yield 70%.

*Anal.* Calcd. for C<sub>22</sub>H<sub>26</sub>NO<sub>2</sub>I: C, 56.52; H, 6.47; N, 3.00. Found: C, 56.21; H, 6.75; N, 3.25.

$\alpha$ -[*p*-(*p*-Methoxyphenyl)-phenyl]- $\alpha$ -methyl-2-piperidine-methanol.—Three grams of the pyridinecarbinol as its hydrochloride in 30 ml. of methanol was hydrogenated over 200 mg. of platinum oxide at room temperature and 300 lb. pressure of hydrogen. The solution was filtered from the catalyst, concentrated and diluted with ether to precipitate the hydrochloride. It was purified by recrystallization from methanol-acetone; m.p. 264-265°, yield 100%.

*Anal.* Calcd. for C<sub>21</sub>H<sub>23</sub>NO<sub>2</sub>Cl: C, 69.75; H, 7.80; N, 3.87. Found: C, 68.74; H, 7.62; N, 3.80.

When the salt is converted to the free base in the usual manner, it is obtained as white feathery needles, m.p. 165-167°.

*Anal.* Calcd. for C<sub>21</sub>H<sub>27</sub>NO<sub>2</sub>: C, 77.50; H, 8.37; N, 4.31. Found: C, 77.46; H, 8.36; N, 4.50.

$\alpha$ -[*p*-(*p*-Methoxyphenyl)-benzyl]- $\alpha$ -methyl-2-pyridine-ethanol.—The  $\alpha$ -picolyllithium was prepared in the usual way from 2.48 g. (0.016 mole) of bromobenzene, 1.6 ml. (0.016 mole) of *o*-picoline and 0.22 g. (0.032 g. atom) of lithium in 25 ml. of dry ether was slowly added. The red color of the solution was discharged and a yellow precipitate formed. After 1 hour stirring at 0.5°, 25 ml. of water was added followed by 10 ml. of hydrochloric acid. The reaction mixture was set aside at 5° for 18 hours and the solid filtered off. It was dried by azeotropic distillation of benzene and then recrystallized from ethanol to yield yellow crystals, m.p. 190-191°, yield 52%.

*Anal.* Calcd. for C<sub>22</sub>H<sub>24</sub>NO<sub>2</sub>Cl·H<sub>2</sub>O: C, 68.15; H, 6.71; N, 3.61. Found: C, 68.42; H, 6.44; N, 3.94.

$\alpha$ -[*p*-(*p*-Methoxyphenyl)-benzyl]- $\alpha$ -methyl-2-pyridine-ethanol Methiodide.—The free base obtained from 10 g. of the above salt was refluxed in 40 ml. of methanol with 15 ml. of methyl iodide for 5 days and concentrated *in vacuo*. The red oil crystallized upon standing and was recrystallized from ethanol until pure, m.p. 182-185°; yellow crystals, yield 69%.

*Anal.* Calcd. for C<sub>22</sub>H<sub>26</sub>NO<sub>2</sub>I: C, 58.10; H, 5.59; N, 2.95. Found: C, 58.30; H, 5.42; N, 2.84.

$\alpha$ -[*p*-(*p*-Methoxyphenyl)-benzyl]- $\alpha$ ,1-dimethyl-2-piperidine-ethanol.—A 20-g. suspension of the above methiodide was reduced in 200 ml. of ethanol over 0.5 g. of platinum oxide under 200 lb. pressure of hydrogen at room temperature. The solution was filtered from the catalyst, the solvent evaporated *in vacuo* and the residue converted to the free base with dilute alkali. The red oil was extracted with ether and then distilled *in vacuo*, b.p. 195-205° at 0.05 mm., and obtained as a very thick yellow sirup; yield 61%.

*Anal.* Calcd. for C<sub>23</sub>H<sub>31</sub>NO<sub>2</sub>: C, 78.20; H, 8.84; N, 3.96. Found: C, 78.52; H, 8.98; N, 4.00.

$\alpha$ -[*p*-(*p*-Methoxyphenyl)-benzyl]- $\alpha$ -methyl-2-piperidine-ethanol.—A suspension of 7.4 g. of the corresponding pyridine hydrochloride in 40 ml. of methanol over 250 mg. of platinum oxide was reduced at room temperature under 500 lb. pressure of hydrogen. After filtering and evaporating the solvent, the free base was liberated in the usual manner and extracted with chloroform. From the chloroform, the product was obtained crystalline and was recrystallized from ethanol; m.p. 148-152°, yield 71%.

*Anal.* Calcd. for C<sub>23</sub>H<sub>29</sub>NO<sub>2</sub>: C, 77.84; H, 8.61; N, 4.16. Found: C, 77.77; H, 8.59; N, 4.06.

**Biological Studies.**—The bases were tested as their water-soluble hydrochlorides. These compounds were screened by the Pharmacology Department.<sup>12</sup> The majority of the compounds are weak vasodepressor agents; doses of 4 mg./kg., i.v. in anesthetized dogs caused only fleeting depressions of the blood pressure. No effects were observed on the

(12) We are indebted to Dr. Lowell O. Randall and his associates for these results.

blood pressure responses to epinephrine, acetylcholine, carotid occlusion or peripheral vagus stimulation. Two of the compounds, 7 and 15, showed anti-serotonin activity in that they blocked the pressor effect of serotonin in dogs at the dose level of 4 mg./kg. None of the compounds inhibited the bronchoconstriction in cats induced by serotonin. None had significant ganglionic or neuromuscular blocking activity in cats.

NUTLEY, N. J.

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

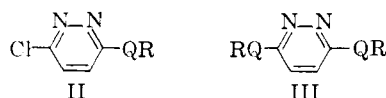
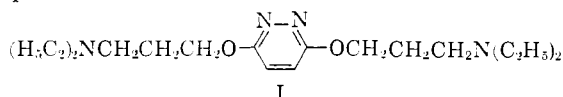
## Pyridazine Derivatives. V.<sup>1,2</sup> Some Ethers and Thioethers Derived from 3,6-Dichloropyridazine

BY EDGAR A. STECK<sup>3</sup> AND R. PAULINE BRUNDAGE

RECEIVED MAY 14, 1959

The greater number of pyridazine 3,6-bis-ethers, which were made for eventual pharmacological trials, contained basic groups. Certain other 3-chloro-6-pyridazyl ethers and thioethers were also prepared, as well as some of the bis-thioether types.

The detailed pharmacological evaluation of the bis-quaternary salts of 3,6-bis-(dialkylaminoalkoxy)-pyridazines, together with kindred thioethers,<sup>1c</sup> has established<sup>4-6</sup> that the series has novel patterns of neuromuscular blocking action. The greatest potency was found in the quaternary ammonium salts of I. Continuing interest was fostered by these results, and the present contribution relates to various ethers and thioethers which were prepared from 3,6-dichloropyridazine. In certain instances, it was readily possible to obtain the intermediate II, but the greater attention was devoted to the 3,6-bis-substituted pyridazines III. The basically-substituted derivatives of III were of especial interest, and variations in activity with modifications in character of the attachment and nature of quaternizing agents were fundamental aspects of the work.



where Q is O or S and R is a group, alkyl, aralkyl or heteryl in nature

The nucleophilic displacement of one chlorine in 3,6-dichloropyridazine by reaction with alkoxides or phenoxides under mild conditions readily produced several representatives of II. These findings are in accord with recent reports.<sup>7-9</sup> Partial

(1) Previous contributions: E. A. Steck, R. P. Brundage and L. T. Fletcher, *THIS JOURNAL*, (a) **75**, 1117 (1953); (b) **76**, 3225 (1954); (c) **76**, 4454 (1954).

(2) E. A. Steck, *J. Org. Chem.*, in the press.

(3) McNeil Laboratories, Philadelphia 32, Penna.

(4) R. M. Gesler and J. O. Hoppe, *Federation Proc.*, **15**, 427 (1946).

(5) R. M. Gesler and J. O. Hoppe, *J. Pharmacol. Exptl. Ther.*, **116**, 22 (1956); **118**, 388, 395 (1956).

(6) R. M. Gesler, A. V. Lasher, J. O. Hoppe and E. A. Steck, *ibid.*, **125**, 323 (1959).

(7) J. Druey, K. Meier and K. Eichenberger, *Helv. Chim. Acta*, **37**, 121 (1954).

(8) T. Itai and H. Igeta, *J. Pharm. Soc., Japan*, **74**, 1195 (1954).

(9) N. Takahayashi, *ibid.*, **75**, 778, 1296 (1956).

hydrolysis of the halide to 6-chloro-3-pyridazine<sup>7</sup> was achieved in acid medium (*cf.* ref. 10).

Symmetrical ethers (and thioethers, to a lesser extent) having the structure III were of particular interest as potential pharmacodynamic agents. In light of previous work,<sup>1c,4-6</sup> the ethers having basic centers formed the core of the program. The sodio (or potassio) derivatives of the hydroxy compounds were caused to act upon 3,6-dichloropyridazine in xylene for the preparation of the series summarized in Table I. The first few examples were synthesized as variants of 3,6-bis-(methoxy)-pyridazine, a compound reported since completion of this work.<sup>7,8,11</sup> All other compounds in the group of bis-ethers were made for the investigation of the interrelations existing between structure and activity of the salts of these pyridazines. In several instances, it was somewhat difficult to consider that there was maximal possible extension between the basic centers of the basic ethers in attempting a structure-activity relationship as neuromuscular blocking agents. We had previously<sup>1c</sup> remarked on the indications which have been gleaned in this regard on the distance between the two quaternary centers. As in our earlier work,<sup>1c</sup> we have here refrained from choosing a specific structure for the salts of the thioethers, but have tacitly considered that these are bis-quaternary salts involving the terminal chain nitrogens. The quaternizing agents employed were the customary ones. Certain additional salts were made from bases which we described previously<sup>1c</sup> to admit of further study (*cf.* refs. 4-6). As an example of another formation of the type III, the nucleophilic reagent sodium 2-diethylaminoethoxide acted upon 3-chloro-6-methoxypyridazine to produce the lower homolog of I by displacement of the methoxy group (*cf.*, *inter alia*, refs. 7, 9, 10, 12).

3,6-Dichloropyridazine was subjected to reaction with excess of thiourea, followed by dilute caustic, toward obtaining 3,6-dithiopyridazine. The product, however, was an excellent yield of a

(10) J. F. Bunnett and R. E. Zahler, *Chem. Revs.*, **49**, 273 (1951).

(11) J. Druey, U. S. Patent 2,764,584.

(12) K. Eichenberger, A. Staehelin and J. Druey, *Helv. Chim. Acta*, **37**, 837 (1954).