intermediate with an ethanolic solution of hydroxylamine in the customary manner, a mass of colorless rods separated from the reaction mixture and were removed by filtration; weight 5.31 g. Solution of this salt in 5% sodium hydroxide solution followed by acidification with hydrochloric acid led to the crystalline oximino acid which amounted to 4.53 g. (82%); m.p. 167° with evolution of gas.

An analytical sample was obtained as colorless clusters of needles by recrystallization from hot water followed by a wash of the dried crystals with boiling benzene; m.p. 166° with evolution of gas.

Anal. Calcd. for $C_{11}H_{10}N_4O_3$: C, 53.66; H, 4.09; N, 22.76. Found: C, 54.04, 54.21; H, 4.10, 4.17; N, 23.06, 22.84.

1-Phenyl-1,2,3-triazole-4-acetonitrile.—The oximino acid (4.06 g., 0.0165 mole) was added to a chilled mixture of 1.35 g. of fused sodium acetate in 16.5 ml. of acetic anhydride. On allowing the temperature to rise, a vigorous reaction took place below 45°. After most of the solvent had been removed by concentration under reduced pressure, treatment with dilute sodium hydroxide solution to *p*H 8 gave 2.94 g. (97%) of colorless needles, m.p. 95.5–96.5°.

Recrystallization from a mixture of benzene and petroleum ether afforded an analytical sample melting at 95–96°.

Anal. Calcd. for $C_{10}H_8N_4$: C, 65.20; H, 4.38; N, 30.42. Found: C, 65.49; H, 4.82; N, 30.70.

This nitrile is soluble in ethanol, acetone, benzene, and in hot water.

1-Phenyl-1,2,3-triazole-4-ethylamine Dihydrochloride.—Hydrogenation of the nitrile (2.76 g., 0.0150 mole) and subsequent hydrolysis of the product was carried out in the usual manner.[2] A quantitative yield (3.90 g.) of crystalline amine dihydrochloride was obtained by concentration of the aqueous solution; m.p. beginning at about 182° with slow evolution of gas. Recrystallization from methanol–ether gave a 73% recovery (2.86 g.) as colorless rods, m.p. 198° with slow evolution of gas; the melting point of this compound is difficult to reproduce as it varies over a 20° range depending on the rate of heating. A second recrystallization afforded an analytical sample with the same melting point when taken simultaneously.

Anal. Calcd. for $C_{10}H_{12}N_4 \cdot 2HCl$: C, 45.99; H, 5.40; N, 21.46. Found:[16] C, 46.27; H, 5.33; N, 21.62.

(16) Values corrected for 0.25% ash.

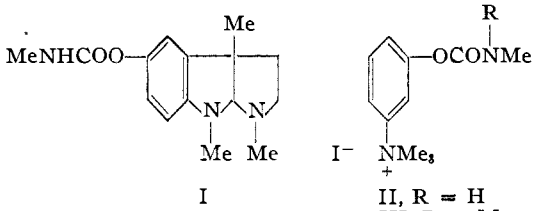
CAMBRIDGE 39, MASSACHUSETTS
RECEIVED AUGUST 15, 1950

[CONTRIBUTION FROM THE WARNER INSTITUTE FOR THERAPEUTIC RESEARCH]

Some Derivatives of 3-Pyridol with Parasympathomimetic Properties[1]

BY H. M. WUEST AND E. H. SAKAL

The discovery by Stedman and his co-workers[2] that quaternary salts of the N-methylurethans of 3-dialkylaminophenols had physostigmine-like parasympathomimetic activity, opened the way to further synthetic work in the field by other investigators.

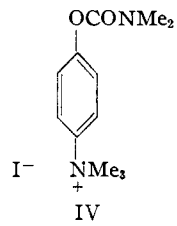


I

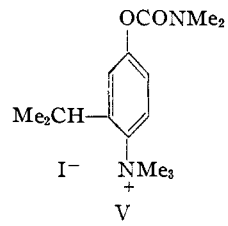
II, R = H
III, R = Me

Stedman's "meta" compound (II) was as unstable as physostigmine (I) in aqueous solution. This led Aeschlimann and Reinert[3] to produce a more stable derivative, such as III which, though somewhat less toxic than II, retained a high order of activity. Later, Stevens and Beutel[4] showed that the introduction of nuclear alkyl groups considerably increased the toxicity in mice of the comparatively inactive 4-dimethylaminophenol derivatives higher toxicity being due, presumably, to increased parasympathomimetic activity. Thus V was five hundred times more toxic than IV.

Recently, Haworth, Lamberton and Woodcock[5] applied the idea of nuclear alkylation to the 3-dimethylaminophenol series, synthesizing such compounds as the 4-methyl and the 2-methyl-5-isopropyl derivatives of II. Both these derivatives were found to be four times as toxic to mice as II.

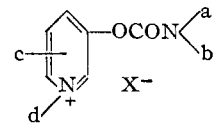


IV



V

The investigation described in the present communication was started with the object of preparing some derivatives of hydroxypyridines with parasympathomimetic activity of possible therapeutic usefulness. 3-Pyridol was selected as the key starting material and a number of derivatives were synthesized, using the general structure VI as a point of departure.



VI

Only two compounds related to this general class have been previously reported. In 1941 Stevens and Beutel[4] listed the dimethylcarbamate of 3-pyridol hydrochloride with its analysis, melting point and LD_{50} in mice (120 mg./kg.) in a table featuring the hydrochlorides and methiodides of some substituted carbamic esters of dimethylaminophenol derivatives. The conspicuous absence, in the table, of the dimethylcarbamate of 3-pyridol methiodide attests the stubborn resistance to crystallization of a number of pyridinium salts of this type. More recently Haworth, Lamberton and Wood-

(1) Presented before the Division of Medicinal Chemistry at the 115th Meeting of the American Chemical Society, San Francisco, Calif., March 27–April 1, 1949.

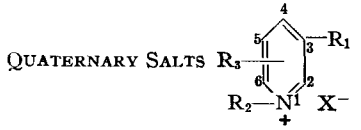
(2) Stedman and co-workers, *Biochem. J.*, **20**, 719 (1926); *ibid.*, **21**, 1902 (1927); *ibid.*, **25**, 1147 (1931); *ibid.*, **26**, 1214 (1932); *Proc. Roy. Soc.* (*London*), **121B**, 142 (1936).

(3) Aeschlimann and Reinert, *J. Pharmacol.*, **43**, 413 (1931).

(4) Stevens and Beutel, THIS JOURNAL, **63**, 308 (1941).

(5) Haworth, Lamberton ann Woodcock, *J. Chem. Soc.*, 182 (1947).

TABLE I

QUATERNARY SALTS 

Number	R_1	R_2	R_3[a]	X	Reacn. temp.,[b] °C.	Reacn. time	M.p.,[bb] °C.	Yield on T-base, %	Nitrogen, % Calcd.	Nitrogen, % Found	Halogen, % Calcd.	Halogen, % Found	In vitro inhibn. of cholinesterase at 3×10^{-9} mole/cc.,[d] ratio	Toxicity in mice[c] LD_{50}, mg./kg. (I. V.)	Activity on *in situ* intestine of anaesthetized dog.[e] Dose required of contraction, mg./kg.
1	$-OCONMe_2$	Methyl[c]	H	Cl	100	48 hr.	174–175	90	12.93	12.79	16.37	16.37	>1/7	1.75	1.0
2	$-OCONMe_2$	Ethyl	H	Br	60	4 days	120–122	73	10.18	10.40	29.04	29.23	>1/6	....	1.0 var.
3	$-OCONMe_2$	*n*-Propyl	H	Br	80	3 days	Oil	96	9.69	9.41	27.64	27.54	1/7	4.5	0.5 var.
4	$-OCONMe_2$	Isopropyl	H	Br	80	6 days	Oil	37	9.69	9.86	27.64	27.93	1/15	4.5	1.0
5	$-OCONMe_2$	*n*-Butyl	H	Br	80	15 hr.	Oil	40	9.24	9.10	26.35	26.34	>1/6	...	0.5
6	$-OCONMe_2$	*n*-Amyl	H	Br	80	3 days	Oil	82	8.83	8.80	25.19	25.06	<1/7	2.0	1.0
7	$-OCONMe_2$	*n*-Hexyl	H	Br	80	20 hr.	Oil	17	8.46	8.76	24.13	24.34	>1/15	5.0	2.0
8	$-OCONMe_2$	*n*-Heptyl	H	Br	80	20 hr.	Oil	18	8.11	8.26	23.15	22.88	>1/15	...	2.0 inact.
9	$-OCONMe_2$	2-Hydroxyethyl	H	Cl	111	8 hr.	130–133	46	11.36	11.45	14.37	14.13	>1/7	2.0	0.05
10	$-OCONMe_2$	Benzyl[d,e]	H	Br	80	1 hr.	116–118	90	8.31	8.29	23.70	23.70	1	0.25	0.1
11	$-OCONMe_2$	4-NO_2-Benzyl	H	Br	25	15 days	104	60	10.99	10.79	20.91	20.82	1	0.4	0.1
12	$-OCONMe_2$	4-MeO-Benzyl	H	Br	25	48 hr.	AHS	22	7.63	7.68	21.76	21.57	>1/7	2.0	1.0 (0.5 var.)
13	$-OCONMe_2$	2-Naphthyl-methyl	H	Cl	80	6 days	AHS	33	8.17	8.41	10.34	10.21	1	...	0.1
14	$-OCONMe_2$	2-Phenylethyl	H	Br	80	3 hr.	Oil	22	7.98	8.08	22.75	22.48	1	0.6	0.2(not minim.)
15	$-OCONMe_2$	2-Thienylmethyl	H	Cl	80	14 hr.	148–149	38	9.39	9.40	11.87	11.75	1	...	1.0 var.
16	$-OCONMe_2$	Benzhydryl	H	Br	80	19 hr.	201–203	66	6.78	6.86	19.33	19.55	<1/75	...	...
17	$-OCONMe_2$	Allyl	H	Br	80	5 hr.	Oil	95	9.76	9.59	27.83	27.60	1/4	4.0	1.0
18	$-OCONMe_2$	Methallyl	H	Br	25	2 days	Oil	66	9.30	9.28	26.53	26.36	<1/7	2.5	1.0 var.
19	$-OCONMe_2$	Methylene (bis-cmpd.)[f]	H	Br	100	4 hr.	208–209	5	11.07	10.79	31.58	31.65	<1/33	...	...
20	$-OCONMe_2$	1,2-Ethylene (bis-cmpd.)[g]	H	Br	125–135	3 hr.	239–240	27	10.77	10.80	30.73	30.63	>1/4	...	0.5
21	$-OH$	Benzyl	H	Br	80	3 hr.	133–136	62	5.26	5.28	30.03	30.30	<1/75	750.0	1.0 inact.
22	$-OCOMe$	Methyl	H	I	25	3 days	114–117	53	5.02	5.06	45.48	45.44	<1/75	250.0 Non-toxic	3.0
23	$-OCONHMe$	Benzyl	H	Br	25	3 days	122[h]	33	8.67	8.44	24.73	24.84	<1/75	...	...
24	$-OCONEt_2$	Benzyl	H	Br	25	5 days	AHS	60	7.67	7.45	21.88	21.77	<1/75	25.0	2.0 inact.
25	$-OCON(Me)CH_2Ph$	Benzyl	H	Br	80	3 hr.	136–137	74	6.78	7.08	19.33	19.33	>1	...	0.2
26	$-OCON-(CH_2Ph)_2$	Benzyl	H	Br	80	1 hr.	144–145[h]	67	5.72	5.86	16.33	16.47	....	...	1.0 inact.
27	$-OCON(Me)p-ClC_6H_4$	Benzyl[i]	H	Br	75		144–149	50	6.46	6.55	18.43	18.50	>1	...	0.5
28	$-OCONPh_2$	Methyl		Br	25	15 hr.	219–221	58	7.27	7.04	20.75	20.97	....	...	1.0 inact.
29	$-OCON(CH_2)_4$[k]	Benzyl[j]	H	Br	80	6 hr.	162–164	66	7.71	7.76	22.00	22.03	<1/30	...	0.25

TABLE I (*Continued*)

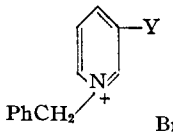
Number	R_1	R_2	R_3[a]	X	Reacn. temp.,[b] °C.	Reacn. time	M.p.,[bb] °C.	Yield on T base, %	Nitrogen, % Calcd.	Nitrogen, % Found	Halogen, % Calcd.	Halogen, % Found	In vitro inhibn. of chlorinesterase at 3×10^{-9} mole/cc.,[a] ratio	Toxicity in mice[g] LD_{50} mg./kg. (I. V.)	Activity on *in situ* intestine of anaesthetized dog.[g] Dose required of contraction, mg./kg.
30	$-OCON(CH_2)_2-O-(CH_2)_2$[m]	Benzyl	H	Br	80	1.5 hr.	127–128	42	7.39	7.27	21.07	21.17	<1/75	7.0	...
31	$-OSO_2NMe_2$	Benzyl[r]	H	Br	80	6 hr.	155	64	7.51	7.66	21.40	21.24	<1/75	...	0.1 to 1.0 (erratic)
32	$-SCONMe_2$	Benzyl	H	Br	80	2 hr.	147-148	32	7.93	7.77	22.63	22.81	1/15	10	1.0
33	$-OCONMe_2$[n]	Benzyl	6-Methyl	Br	80	1 hr.	204-206	80	7.98	7.69	22.75	22.92	>1/7	...	0.2
34	$-OCONMe_2$	Benzyl	6-Styryl[p]	Br	65	4 hr.	198-199	34	6.38	6.36	18.19	18.18	<1/75	...	0.5 inact.
35	H	Benzyl	2,6-Dimethyl	Br	80	5 hr.	185–187	25	5.04	4.86	28.73	29.00	....	...	...
36	$-OCONMe_2$	Methyl	2,6-Dimethyl	Br	65	9 days	112-114	35	9.69	9.60	27.64	27.63	>1/4	0.12	0.5
37	$-OCONMe_2$	Methyl	2,4,6-Trimethyl	I	100	4 hr.	198–199	46	8.00	7.86	36.24	36.18	1/30	...	1.0
38	$-OCONMe_2$	Methyl	2,4,5-Trimethyl	I	25	3 days	196-198	72	8.00	7.80	36.24	35.98	....	...	...
39	$-OCONMe_2$	Benzyl	2,4,5-Trimethyl-6-benzyl	Br	25	9 days	124-125	49	5.97	5.62	17.03	17.67[q]	<1/75	...	...
40	$-OCONMe_2$	Methyl	2-Iodo	I	70	3 days	171–172	67	6.46	6.49	29.24	29.16	>1	0.15	0.025
41	$-OCONHMe$	Methyl	2-Iodo	I	25	24 hr.	153–154	10	6.67	6.47	30.22	30.49	....	...	2.0 inact.

[a] One or more nuclear substituents other than R_1 and R_2. [bb] Melting points are uncorrected. AHS is abbreviation for amorphous, hygroscopic solid whose m.p. is not conveniently determined. [b] In several cases mild conditions were used deliberately to show up the unreactivity of the organic halide. Further, it should be borne in mind that chlorides require more drastic conditions than bromides. [c] The following analogs of this compound were also prepared: (1) X = Br; m.p. 154–155° (77% yield at room temperature). *Anal.* Calcd. for $C_{19}H_{18}BrN_2O_2$: N, 10.72; Br, 30.61. Found: N, 10.44; Br, 30.51. (2) X = $C_6H_2N_3O_7$ (picrate); m.p. 155–166°. *Anal.* Calcd. for $C_{25}H_{25}N_5O_9$: C, 44.01; H, 3.69; N, 17.11. Found: C, 44.28; H, 3.72; N, 17.3. [d] Compound No. 10 was taken as the standard of comparison in the determination of anticholinesterase activity. A substance is rated one-tenth as active if a 1×10^{-9} mole/cc. solution causes the same percentage inhibition as a 1×10^{-10} mole/cc. solution of the standard. [e] The following analogs of this compound were also prepared: (1) X = Cl; m.p. 118–120° (45% yield). *Anal.* Calcd. for $C_{15}H_{17}ClN_2O_2$: N, 9.55; Cl, 12.11. Found: N, 9.28; Cl, 11.98. (2) X = $C_6H_2N_3O_7$ (picrate); m.p. 120–121°. *Anal.* Calcd. for $C_{21}H_{19}N_2O_9$: C, 51.96; H, 3.95; N, 14.43. Found: C, 52.36; H, 4.23; N, 14.14. (3) X = $OPO(OH)_2$ (dihydrogen phosphate); m.p. 145–146°. *Anal.* Calcd. for $C_{15}H_{19}N_2O_6P$: N, 7.93; P, 8.77. Found: N, 7.19; P, 8.22. [f] Methylene bis-[1-(3-dimethylcarbamyloxy)-pyridinium bromide]. [g] 1,2-Ethylene bis-[1-(3-dimethylcarbamyloxy)-pyridinium bromide]. [h] Melts with decomposition. [i] The following analogs of this compound were also prepared: (1) R_2 = methyl; m.p. 180–182°. *Anal.* Calcd. for $C_{14}H_{14}BrClN_2O_2$: N, 7.83; Br, 22.16. (2) R_2 = *n*-propyl; AHS. *Anal.* Calcd. for $C_{16}H_{18}BrClN_2O_2$: N, 7.26; Br, 20.72. Found: N, 7.11; Br, 20.97. (3) R_2 = *n*-amyl; AHS. *Anal.* Calcd. for $C_{18}H_{22}BrClN_2O_2$: N, 6.77; Br, 19.35. Found: N, 6.94; Br, 19.40. (4) R_2 = *n*-hexyl; AHS. *Anal.* Calcd. for $C_{19}H_{24}BrClN_2O_2$: N, 6.55; Br, 18.68. Found: N, 6.53; Br, 18.45. [j] The analog of this compound where R_2 = methyl was also prepared: m.p. 130–133°. *Anal.* Calcd. for $C_{11}H_{15}BrN_2O_2$: N, 9.75; Br, 27.83. Found: N, 9.74; Br, 28.03. [k] N,N-Tetramethylenecarbamyloxy. [m] N,N-(3-Oxapentamethylene)-carbamyloxy. [n] The following analogs of this compound were also prepared: (1) R_1 = $-OCON(Me)$-*p*-ClC_6H_4; m.p. 114–117°. *Anal.* Calcd. for $C_{21}H_{20}BrClN_2O_2$: N, 6.26; Br, 17.84; Found: N, 6.20; Br, 17.83. (2) R_1 = $-OCON(Me$-*p*-$Cl-C_6H_4$; R_2 = methyl; m.p. 165–167°. *Anal.* Calcd. for $C_{15}H_{16}BrClN_2O_2$: N, 7.54; Br, 21.51. Found: N, 7.40; Br 21.46. (The synthesis of this compound is described in the experimental section.) (3) R_2 = methyl; m.p. 150–152° (active on the dog intestine at 2.0 mg./kg.). *Anal.* Calcd. for $C_{10}H_{15}O_2N_2Br$: N, 10.18; Br, 29.04. Found: N, 10.38; Br, 29.02. [p] This compound is obtained by refluxing a methanol solution of compound No. 33 with benzaldehyde, in the presence of piperidine. [q] The stubborn contaminant most probably consists of traces of 1-benzyl-3-dimethylcarbamyloxy-2,4,5-trimethylpyridinium bromide. [r] The analog of this compound where R_2 = methyl was also prepared, m.p. 160–162°. *Anal.* Calcd. for $C_{16}H_{13}N_2O_3S$: N, 9.43; Br, 26.88. Found: N, 9.25; Br, 27.11. [s] These results were supplied by Dr. N. Evcoli and Dr. R. J. Schachter, who will report their findings in detail elsewhere.

cock[5] included the phenylcarbamate of 3-pyridol methiodide with its melting point and analysis, as the sole pyridine derivative in a long list of quaternary salts.

The compounds shown in Table I were obtained by the following general procedure: condensation of the various pyridols with the appropriate acid chlorides in the presence of triethylamine gave rise to substituted carbamic esters (see Table III); these were then converted to quaternary pyridinium salts upon treatment with organic halides. The arrangement of compounds in Table I represents successive variations of the ester side chain (R_1), quaternizing radical (R_2), and substituent (R_3) in the pyridine nucleus.

Variations of the ester side chain may be divided into three groups represented by VII, VIII and IX. In structure VII, R_1 and R_2, which are not necessarily the same, are selected from among the radi-

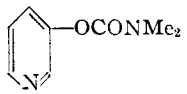


VII, Y = $OCON(R_1)R_2$
VIII, Y = OSO_2NMe_2
IX, Y = $SCONMe_2$

cals H, Me, Et, Ph, $PhCH_2$ and *p*-Cl-C_6H_4, or together (with the amide nitrogen) may form a pyrrolidine or a morpholine nucleus. Structures VIII and IX feature the dimethylsulfamyloxy and dimethylcarbamylmercapto side chain, respectively.

The order of reactivity of the various organic halides employed as quaternizing agents generally conforms with the findings of Menschutkin.[6,7] Thus the reaction rate fell progressively with increasing length of the aliphatic chain with alkyl halides as well as with aralkyl halides. Further, primary halides were more reactive than secondary halides, whilst the tertiary halides used gave no quaternary salts.

Although a variety of organic halides was successfully employed in quaternization reactions in this investigation, methyl and benzyl halides were chiefly used with bases other than X-methyl halides because of their high reactivity and benzyl halides on account of the relatively high biological activity of the resulting quaternary salts.



X

The influence of nuclear substitution in X upon the quaternization reaction varied widely with the nature and position of the substituents. This effect is qualitatively evaluated in Table II in terms of whether the substituted base: (a) is reactive enough to quaternize with both methyl and benzyl halides; (b) reacts only with methyl halides; (c) reacts with neither methyl nor benzyl halides.

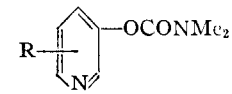
Ortho Effect.—An explanation in terms of steric hindrance, of the ortho effect manifested in the quaternization of several of the bases shown in Table II, seems plausible in connection with the iodo, methoxy and nitro derivatives. Thus molecular models show that the strain pro-

(6) Menschutkin, *Z. physik. Chem.*, **5**, 589 (1890): Me, 100; Et, 8.8; *n*-Pr, 1.7; *n*-Bu, 1.2; *n*-Hept., 0.9; *n*-Oct., 0.9.

(7) See also Noller and Dinsmore, THIS JOURNAL, **54**, 1025 (1932).

TABLE II

EFFECT OF NUCLEAR SUBSTITUTION ON QUATERNIZATION REACTION



R (one or more nuclear substituents)	Quaternary methobromide salt	Quaternary benzyl bromide salt
H	+	+
6-Methyl	+	+
2,4,5-Trimethyl	+	+
2,6-Dimethyl	+	−
2,4,6-Trimethyl	+	−
2-Iodo	+	−
2-Methoxy	−	−
2-Nitro	−	−
2,X-Diiodo	−	−

duced by quaternization of these compounds increases in the order indicated. However, the steric effects caused by single or double *o*-methyl substitution is practically negligible in quaternary salts. The fact that 2,6-lutidine forms a well defined quaternary salt with benzyl bromide whereas 3-dimethylcarbamyloxy-2,6-lutidine does not react indicates that the 3-dimethylcarbamyloxy group induces a drop in basicity.

It should be pointed out that in the last four compounds of Table II, resonance of the molecule is probably excluded as a factor affecting the quaternization. Molecular models indicate that steric interaction of vicinal nuclear substituents in these structures discourages the coplanarity essential to the formation of resonance hybrids involving these substituents.[8]

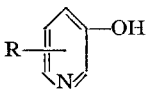
Structure–activity Relationship.—The results of a preliminary pharmacological study of the compounds synthesized indicate that a number of substances conforming to the generic structure VI possess parasympathomimetic properties. In Table I the data have been limited to intravenous toxicity (LD_{50} in mice) and peristaltic action on the intestine of anesthetized dogs.

As in the case of the known parasympathomimetic substances, the biological activity of compounds of formula VI is sensitive to slight variations in the chemical structure. Whereas the dimethylurethan configuration confers the highest activity observed, replacement by diethyl or diphenylurethan results in appreciable reduction of activity. With mixed substituted urethans where a is methyl and b is either aryl or aralkyl, the activity is moderate; whereas if a is methyl and b is hydrogen no activity is observed.[9] Compounds in which the "ether oxygen" is replaced by sulfur or the carbonyl group by SO_2, retain a moderate activity. Regarding substitution in the pyridine nucleus, the introduction of an iodine atom in the 2-position is attended by a considerable potentiation of biological action (Table I: No. 40 is twelve times as toxic and forty times as active as No. 1); whereas substitution by one, two

(8) *Cf.*, Wheland, Brownell and Mayo, *ibid*, **70**, 2492 (1948); and Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1948, p. 222.

(9) Compound 41 in Table I was tested in *p*H 4 buffer solution (to minimize decomposition) and found inactive in the dog at 2 mg./kg. This observation contrasts with those of previous workers[2,3,4,5] who found that monomethyl urethan radical confers high biological activity in the *dimethylaminophenol* series.

TABLE III

INTERMEDIATES R— 

R	M.p., °C.	Acid chloride	B.p. or m.p., °C.	Mm.	Ester b.p. or m.p., °C.	Mm.	Yield on pyridol, %	Molecular formula	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Nitrogen, % Calcd.	Found	Halogen, % Calcd.	Found
H[a]	127	MeCOCl	51–52		43–44	0.21[b]	91	$C_7H_7NO_2$	...	...	..	..	10.21	10.09		
H[a]	127	MeNCO	43–45		.....	[c]	100	$C_7H_8N_2O_2$	55.25	54.91	5.30	5.83	18.41	18.08		
H[a]	127	Me_2NCOCl[d]	166		90	0.25	92	$C_8H_{10}N_2O_2$	57.81	58.02	6.06	6.10	16.86	16.97		
H[a]	127	Et_2NCOCl[e]	68–70	10	82–84	0.1	86	$C_{10}H_{14}N_2O_2$	61.83	61.79	7.26	7.40	14.43	14.29		
H[a]	127	$PhCH_2N(Me)COCl$[f]	92–94	0.3	152–154	0.3	75	$C_{14}H_{14}N_2O_2$	69.40	69.29	5.82	5.80	11.57	11.27		
H[a]	127	$(PhCH_2)_2NCOCl$[g]	164–165	0.5	182–185	0.15	86	$C_{20}H_{18}N_2O_2$	75.45	75.33	5.70	5.42	8.80	9.00		
H[a]	127	p-$ClC_6H_4N(Me)COCl$[h]	M. 65–68		186–188	2	94	$C_{13}H_{11}ClN_2O_2$	...	...	..	..	10.66	10.55	13.37	13.52
H[a]	127	Ph_2NCOCl[i]	M. 85–86		M. 112–114		76	$C_{18}H_{14}N_2O_2$	74.47	74.74	4.86	4.92	9.66	9.48		
H[a]	127	$(CH_2)_2$—$(CH_2)_2NCOCl$[j]	62	1.5	M. 64–66		85	$C_{10}H_{12}N_2O_2$	62.49	62.37	6.30	6.12	14.55	14.30		
H[a]	127	$(CH_2)_2$—O—$(CH_2)_2NCOCl$[k]	110	11	M. 71–73		77	$C_{10}H_{12}N_2O_3$	57.69	57.97	5.81	5.81	13.45	13.65		
6-Methyl[k]	167–170	Me_2NCOCl[d]	166		98	0.45	89	$C_9H_{12}N_2O_2$	59.98	59.68	6.62	6.54	15.55	15.38		
6-Methyl[k']	167–170	p-$ClC_6H_4N(Me)COCl$[h]	M. 65–68		182–185	2.5	80	$C_{14}H_{13}ClN_2O_2$	...	...	..	..	10.13	9.96	12.83	12.66
2,6-Dimethyl[m]	208–210	Me_2NCOCl[d]	166		78–79	0.15	75	$C_{10}H_{14}N_2O_2$	61.83	62.13	7.26	7.43	14.43	14.53[n]		
2,4,6-Trimethyl[p]	131–133	Me_2NCOCl[d]	166		92–93	0.2	78	$C_{11}H_{16}N_2O_2$	63.44	63.57	7.75	7.53	13.45	13.43		
2,4,5-Trimethyl[q]	173–176	Me_2NCOCl[d]	166		109–112.0	0.5	41	$C_{11}H_{16}N_2O_2$	63.44	62.72[q']	7.75	7.51	13.45	13.22		
2-Chloro[r]	167–168.5	Me_2NCOCl[d]	166		M. 99–100		75	$C_8H_9ClN_2O_2$	...	...	..	..	13.97	14.14	17.67	17.47
2-Iodo[r]	188–190	Me_2NCOCl[d]	166		114	0.15	81	$C_8H_9IN_2O_2$	...	...	..	..	9.59	9.56	43.45	43.59
2-Iodo	188–190	MeNCO	43–45		M. 111–114.5		55	$C_7H_7IN_2O_2$	...	...	..	..	10.08	10.06	45.64	45.67
2,X-Diiodo[s]	194–196	Me_2NCOCl[d]	166		M. 90.5–92		65	$C_8H_8I_2N_2O_2$	...	...	..	..	6.70	6.65	60.73	60.87
2-Nitro[t]	68–70	Me_2NCOCl[d]	166		M. 189–192		64	$C_8H_9N_3O_4$	45.50	45.81	4.30	4.30	19.90	19.80		
2-Methoxy[r]	67–68	Me_2NCOCl[d]	166		M. 58		66	$C_9H_{12}N_2O_3$	55.09	55.32	6.17	6.43	14.28	14.24		
H[a]	127	Me_2NSO_2Cl[u]	80–85	16	116.5–118	1	65	$C_7H_{10}N_2O_3S$	...	...	..	..	13.84	13.64		
H (mercapto)[v]	78–80	Me_2NCOCl[d]	166		113–115	0.3	81	$C_8H_{10}N_2OS$	52.74	52.46	5.53	5.64	15.38	15.22		

[a] Fischer and Renouf, *Ber.*, **17**, 763 (1884). Samples of this material were kindly prepared for us by Mr. E. H. Kastning and Dr. G. C. van Wessem. [b] *Ibid.*, **17**, 1897 (1884) give b.p. 210°. [c] Yellow oil, not distilled; prepared by dissolving 3-pyridol in 3 mole-equivalents of MeNCO, allowing to stand for 12 hours and removing the excess MeNCO *in vacuo*. [d] Hantzsch and Sauer, *Ann.*, **299**, 85 (1898). [e] Boon, *J. Chem. Soc.*, 307 (1947). [f] Prepared in 61% yield by reacting phosgene with N-methylbenzylamine in benzene solution in the presence of pyridine, at *ca.* 2–5°. Calcd. for $C_9H_{10}ClNO$: N, 7.63; Cl, 19.32. Found: N, 7.73; Cl, 19.17. [g] Prepared in 73% yield by reacting phosgene with dibenzylamine in benzene solution in the presence of pyridine, at *ca.* 2–5°. Calcd. for $C_{15}H_{14}ClNO$: N, 5.39; Cl, 13.66. Found: N, 5.61; Cl, 13.39. [h] Aeschlimann and Stempel, Jubilee Vol., Emil Barell, 311 (1946). [i] Eastman Kodak Co. grade. [j] Prepared in 67% yield by treating phosgene with pyrrolidine in benzene solution, in the presence of pyridine, at *ca.* 2–5°. Calcd. for C_5H_8ClNO: N, 10.48; Cl, 26.56. Found: N, 10.56; Cl, 26.88. [k] Prepared according to Wulff (U. S. Patent 1,880,645). The structure of this substance was established by Parker and Shive, THIS JOURNAL, **69**, 63 (1947), and by Urbanski, *J. Chem. Soc.*, 132 (1947). A sample of this material was kindly prepared for us by Mr. A. De Maria. [m] The synthesis of this compound is described in the experimental section. [n] Nitrogen analysis by Dumas procedure. All others by Kjeldahl. [p] Plazek, *Ber.*, **72B**, 577 (1939). The sample used was kindly prepared by Dr. F. Leonard. [q] Harris, THIS JOURNAL, **62**, 3204 (1940). [q'] Though this substance is slightly impure, it formed a methiodide having a satisfactory analysis (see Table I, No. 38). [r] Schickh, Binz and Schulz, *Ber.*, **69B** 2593 (1936). [s] *Ibid.*, melting point reported is 198°. [t] Plazek and Rodewald, *Roczniki Chem.*, **16**, 502 (1936). [u] Binkley and Degering, THIS JOURNAL, **61**, 3250 (1939). [v] 3-Pyridinethiol. The synthesis of this new compound is described in the experimental section.

or three methyl groups in various positions does not modify the activity appreciably.[10]

Quaternizing radicals (d in formula VI) may be divided essentially into two groups in accordance with the biological potency of the resulting pyridinium salts: (a) primary and secondary alkyl, unsaturated primary aliphatic (allyl, methallyl), primary alkylene (1,2-ethylene); (b) aralkyl (benzyl, 2-phenylethyl, 2-naphthylmethyl) and 2-hydroxyethyl, which stands alone in this group. The salts corresponding to group (b)[11] are about ten times as active as those of group (a).

The fact that the principles evolved from observations of structure–activity relationships in this investigation are not in close accord with those of the dimethylaminophenols series (see footnotes 9, 10 and 11) may be ascribed to the unique position of the nitrogen atom in the pyridine ring. Thus, on account of the orientation of charges induced by this positive pole, 3-pyridol may be said to be equivalent to 2- or 4-dimethylaminophenol rather than to the 3-isomer.

Anticholinesterase Activity.—The measurements of anticholinesterase activity were carried out in the Warburg apparatus using bovine erythrocytes as the source of cholinesterase.[12] The procedure and observations will be reported in detail elsewhere. The data shown in Table I indicate that the compounds of this series possessing high *in vivo* activity are among the strong inhibitors of cholinesterase; however, the correlation is not exact.

Therapeutic Utility.—Among the biologically more active compounds is 1-benzyl-3-(dimethylcarbamyloxy)-pyridinium bromide[13] (Table I, No. 10). Highly encouraging results have been obtained with this substance in the treatment of clinical cases of post-operative abdominal distension and urinary retention.[14]

Experimental[15]

Pyridols.—The compounds were prepared essentially according to published procedures (see Table III footnotes) except for 2,6-dimethyl-3-pyridol, and 3-mercaptopyridine which is a new compound.

Carbamic Esters.—The carbamic esters were prepared by treating the various pyridols with the appropriate carbamyl chlorides in the presence of triethylamine. The products were purified either by distillation or by recrystallization—usually from a mixture of Skellysolve B and alcohol. Two examples are given to illustrate the general procedure.

Quaternary Salts.—The general procedure for the preparation of quaternary pyridinium salts consisted of mixing a solution of the tertiary base in a non-polar solvent such as benzene or toluene, with the appropriate organic halide. If on standing several hours at room temperature no product separated out, the solution was heated to reflux temperature. (In stubborn cases, the mixture of the tertiary base and the organic halide was heated at higher temperatures in the absence of a solvent.) The reaction time and temperature used in each case are indicated in Table I.

The crude product was then separated from the solvent (by decantation or filtration) and purified by dissolving it in absolute alcohol followed by precipitation with ether (other solvent pairs were used in a few cases).

Most of the salts were highly hygroscopic especially in cases where the products were obtained as uncrystallizable, supercooled oils or as amorphous solids. In all cases the material was extensively dried *in vacuo* over phosphorus pentoxide before analysis.

Two examples are given to illustrate the general procedure.

2,6-Dimethyl-3-pyridol.—Platinum oxide catalyst (0.5 g.) was added to a solution of 2-bromomethyl-3-hydroxy-6-methylpyridine hydrobromide[16] (20 g.) in 95% ethanol (200 cc.) and the mixture shaken with hydrogen at atmospheric pressure and room temperature (20°) until one mole-equivalent of hydrogen was taken up (1 hour). After removal of the catalyst, the filtrate was evaporated to dryness *in vacuo* and the residual solid was dissolved in water (25 cc.) and neutralized to *p*H 8.85 with 10 *N* aqueous sodium hydroxide solution. The precipitate was collected on a filter, washed with ice-cold water, air-dried and recrystallized from a mixture of benzene and 95% ethanol. Colorless plates were obtained melting at 208–210°[17]; yield 5.62 g. (65%).

3-Mercaptopyridine.[18]—A mixture of potassium hydroxide (120 g.) and water (50 cc.) was saturated with hydrogen sulfide. After filtration, the solution was evaporated to dryness *in vacuo*. The residual potassium hydrosulfide was further dried overnight in a vacuum desiccator over concentrated sulfuric acid, then dissolved in propylene glycol (450 cc.) at 175°. Copper powder (1.5 g.) and 3-bromopyridine (95 g.) were then added and the mixture was stirred at 175–190° for 20 hours (under a reflux condenser). The potassium bromide was then removed and the filtrate was taken to dryness under reduced pressure (*ca.* 16 mm.) while heating in an oil-bath at 140–175°. The residue was dissolved in water (150 cc.) and then neutralized to *p*H 4.4 with concentrated hydrochloric acid (*ca.* 80 cc.). The resulting mixture was extracted with chloroform (2 × 200 cc.) and the extract was filtered and evaporated to dryness *in vacuo*. The waxy, orange-colored product (41 g.) was recrystallized from a mixture of Skellysolve B (50 cc.) and benzene (30 cc.) and once more from benzene (15 cc.). The bright-yellow, crystalline product melted at 78–80°; yield 9.3 g. (14%). On standing at room temperature in a stoppered bottle the solid tends to become waxy (presumably from surface oxidation to the disulfide).

Anal. Calcd. for C_5H_5NS: neut. equiv., 111.1. Found: neut. equiv., 115.2.

On account of the instability of the material no further analyses were carried out. Esterification was effected on a freshly prepared sample giving an ester (described below) which analyzed correctly.

3-(Dimethylcarbamylmercapto)-pyridine.—Dimethylcarbamyl chloride (15.6 g.) was added, dropwise, over a 10-minute period to a stirred, refluxing solution of freshly prepared 3-mercaptopyridine (8.8 g.) in a mixture of benzene (200 cc.) and triethylamine (9.2 g.). Stirring under reflux was continued for 4 hours. The triethylamine hydrochloride was then removed by filtration and the filtrate was evaporated *in vacuo*. The brown, residual oil was fractionated through a 6-inch Snyder column. A forerun (1.1 g.) was discarded and the main fraction distilled at 113–115° (0.3 mm.). The product, a clear, yellow liquid, crystallized to a yellow solid which melted at 46–47°; yield 11.7 g. (81%).

Anal. Calcd. for $C_8H_{10}N_2OS$: C, 52.74; H, 5.53; N, 15.38; S, 17.60. Found: C, 52.46; H, 5.64; N, 15.22; S, 17.88.

6-Methyl-3-(N-methyl-N-*p*-chlorophenylcarbamyloxy)-pyridine.—A solution of N-methyl-N-*p*-chlorophenylcar-

(10) Again the response of biological activity to changes in the chemical structure is somewhat in contrast to the 3-dimethylaminophenol series[5]: thus substitution by methyl groups (the position being of "secondary importance") *increases* the toxicity fourfold. Further the methiodide of 6-chloro-3-dimethylaminophenol N-methylurethan is one-tenth *as* toxic as the unchlorinated substance.

(11) To our knowledge, the quaternization, with aralkyl halides, in the dimethylaminophenols series has not been reported. We have made several unsuccessful attempts to quaternize the dimethylurethan of 3-dimethylaminophenol with benzyl bromide and with benzyl iodide.

(12) The preparation was purchased from Winthrop-Stearns, Inc.

(13) Stigminene Bromide, Warner brand of benzpyrinium bromide.

(14) Whitaker and Wright, *N. Y. State J. Med.*, **50**, 437 (1950).

(15) All microanalyses herein reported were carried out by Mr. Louis Dorfman and Miss Beatrice Baumgarten in the Microanalytical Laboratory of this Institute.

(16) Prepared according to Urbanski, *J. Chem. Soc.*, 133 (1947).

(17) This substance was synthesized by Plazek, *Ber.*, **72B**, 577 (1939), by nitration of 2,6-lutidine followed by reduction, diazotization and boiling water. The melting point reported is 209°.

(18) This procedure is similar to that used by Thirtle, THIS JOURNAL, **68**, 342 (1946), for the preparation of 2-mercaptopyridine.

bamyl chloride[19] (10.7 g.) in benzene (50 cc.) was added, dropwise, over a period of 20 minutes, to a stirred, refluxing solution of 3-hydroxy-6-methylpyridine[20] (10.7 g.) in a mixture of benzene (500 cc.) and triethylamine (11.5 g.). Stirring under reflux was continued for 6 hours. The triethylamine hydrochloride was then removed by filtration and the filtrate was evaporated *in vacuo*. The residual oil was then distilled through a small column. The product, a pale-yellow oil, b.p. 182–185° (2.5 mm.), crystallized to a white solid m.p. 78–81°; yield 22.2 g. (80%).

Anal. Calcd. for $C_{14}H_{13}ClN_2O_2$: N, 10.13; Cl, 12.83. Found: N, 9.96; Cl, 12.66.

1-Benzyl-3-(dimethylmercapto)-pyridinium Bromide.—Benzyl bromide (2.74 g.) was added to a solution of 3-(dimethylmercapto)-pyridine (2.55 g.) in benzene (10 cc.), and the resulting solution was heated 2 hours under reflux. The yellow solid formed was collected on a filter, washed with benzene and recrystallized twice from a mixture of absolute alcohol and ether. The product, a colorless crystalline solid, melted, at 147–148°; yield 1.6 g. (32%).

Anal. Calcd. for $C_{15}H_{17}BrN_2OS$: N, 7.93; Br, 22.63; S, 9.08. Found: N, 7.77; Br, 22.81; S, 9.37.

1,6-Dimethyl-3-(N-methyl-N-*p*-chlorophenylcarbamyloxy)-pyridinium Bromide.—A solution of 6-methyl-3-(N-methyl-N-*p*-chlorophenylcarbamyloxy)-pyridine (11 g.) in benzene (35 cc.) was added to a solution of methyl bromide (15 g.) in benzene (25 cc.). The solution was allowed to stand at room temperature overnight whereupon a white solid separated out. The crude product was then collected on a filter, washed with benzene and recrystallized from absolute alcohol and ether. Colorless plates m.p. 165–167° were obtained; yield 10.7 g. (72.5%).

Anal. Calcd. for $C_{15}H_{16}BrClN_2O_2$: N, 7.54; Br, 21.51. Found: N, 7.40; Br, 21.46.

(19) See Table III, footnote *h*.

(20) See Table III, footnote *k*.

Acknowledgment.—Technical assistance in experimental work was rendered by Miss Doris Palmer and Mr. A. G. Bilotti.

Summary

3-Pyridol and a number of its derivatives were converted to substituted carbamic esters which, in turn, were quaternized to pyridinium salts. Fifty-three such quaternary salts are reported, embodying successive variations in the ester side-chain, the quaternizing radical and the substituents in the pyridine nucleus.

Several tertiary bases, with α-substituents in the pyridine ring, resisted quaternization; the ortho effect involved is discussed

A number of the pyridinium salts obtained possess physostigmine-like, parasympathomimetic properties and anticholinesterase activity; a brief discussion is presented of the structure–activity relationship.

NEW YORK, N. Y. RECEIVED MAY 24, 1950

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC.]

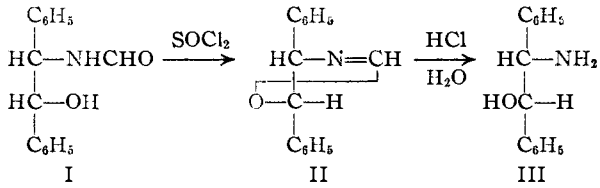
Preparation of the Stereoisomeric α,β-Diphenyl-β-hydroxyethylamines

BY JOHN WEIJLARD, KARL PFISTER, 3RD, EDWARD F. SWANEZY, C. A. ROBINSON AND MAX TISHLER

The preparation of quantities of the stereoisomeric forms of α,β-diphenyl-β-hydroxyethylamine was undertaken in connection with pharmacological study of these compounds as analgesics.[1] Since the literature procedures for the preparation of these compounds are inadequate, we wish to report our experiences in this field.

The high melting racemic modification (m.p. 163°) has been prepared by a number of procedures[2] of which reduction of benzoin oxime appeared most direct. This transformation has been effected in poor yield by sodium amalgam reduction[3] and in better yield by catalytic hydrogenation of the oxime using palladium–sol in dilute ethanol.[4] We prepared this compound in 91% yield by catalytic hydrogenation using palladium-on-charcoal in ethanol containing hydrogen chloride.

The preparation of the lower melting diastereoisomer, known as iso-α,β-diphenyl-β-hydroxyethylamine, was accomplished by inversion of the hydroxyl group *via* oxazoline formation, a procedure successfully applied to the interconversion of threonine and *allo*threonine.[5] In this procedure, N-formyl-α,β-diphenyl-β-hydroxyethylamine (I) is converted to the oxazoline, II, and the latter is hydrolyzed to iso-α,β-diphenyl-β-hydroxyethylamine, III.[6]



No attempt was made to isolate the oxazoline. It is noteworthy that the N-formyl derivative of the iso-α,β-diphenyl-β-hydroxyethylamine (III) did not undergo the inversion reaction under the conditions employed for I. Starting material was mainly recovered in this instance. Under more strenuous conditions, the recovery of starting material was poor but no isomeric hydroxyethylamine, I, was obtained.

The literature on the resolutions of the diastereoisomers of α,β-diphenyl-β-hydroxyethylamine is rather voluminous, particularly so for the lower melting iso racemate. The high melting racemate had been resolved using *d*-oxymethylene camphor

(1) The observation of the morphine-like properties of α,β-diphenyl-β-hydroxyethylamines was made by Dodds, Lawson and Williams, *Nature*, **151**, 614 (1943); *Proc. Roy. Soc. (London)*, **B132**, 119 (1944); *Nature*, **154**, 514 (1944).

(2) Summarized by Lutz, Freek and Murphey, THIS JOURNAL, **70**, 2019 (1948).

(3) Goldschmidt and Polonowska, *Ber.*, **20**, 492 (1887).

(4) Rabe, *ibid.*, **45**, 2166 (1912).

(5) Attenburrow, Elliott and Penny, *J. Chem. Soc.*, 310 (1948); Elliott, *Nature*, **162**, 657 (1948); Pfister, Robinson, Shabica and Tishler, THIS JOURNAL, **70**, 1098 (1948); **71**, 1101 (1949); see also Johnson and Schubert, *ibid.*, **72**, 2187 (1950).

(6) The configuration formulations in this paper are in accord with Fischer's conventions. To effect space economy, only one enantiomorph is given although it should be understood that the second enantiomorph is included when the text refers to the *dl*-form.