[CONTRIBUTION FROM THE RESEARCH DIVISION, U. S. VITAMIN CORPORATION]

# Pyridylethylated Oxazolidinediones[1]

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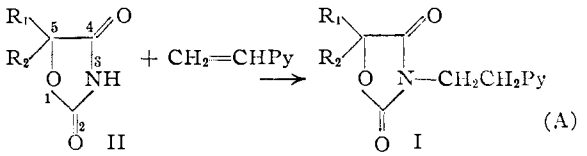
A series of pyridylethylated 2,4-oxazolidinediones of the type I have been synthesized and screened for pharmacological activity. Significant responses found in animals include anticonvulsant activity, depression of motor activity and prolongation of Evipal sleeping time. The results have been assessed in terms of relationship of pharmacological response and chemical structure.

The finding of significant pharmacological activity in a wide variety of pyridylethylated products[2-6] suggested the synthesis and pharmacological investigation of the pyridylethylated oxazolidinediones.

Suitable derivatives of oxazolidinediones[7,8] have found wide clinical utility, particularly as anticonvulsants, and the compounds prepared in this work were screened pharmacologically in animals as anticonvulsants and for their effectiveness as depressors of motor activity.[9]

Pyridylethylation[2] of the oxazolidinediones II proceeded readily without catalyst to yield the 3-pyridylethylated oxazolidine-2,4-diones (I) according to the equation A.




(A)

$R_1$, $R_2$ = H, alkyl, alkylene, aryl; Py = 2-pyridyl, 4-pyridyl, 5-ethyl-2-pyridyl

In contrast to our observations[2] with the pyridylethylated benzoxazine-2,4-diones, the products of type I did not crystallize readily from the reaction mixture, and were either liquids or low-melting solids. It was expedient when purifying to use short path distillation to avoid reversal of equation A to the initial reactants. When the bulk of the $R_1$ or $R_2$ groups (such as phenyl) was such that purification by distillation without considerable reversal of the reaction could not be achieved, it was desirable to convert the impure product to the hydrochloride for subsequent purification.

The 3-pyridylethylated oxazolidinediones which were prepared are described in Table I.

The required oxazolidinediones II, unsubstituted in the 3-position, were prepared by familiar procedures from either the $\alpha$-hydroxy ester[10] or the $\alpha$-hydroxy amide.[11]

The cyanohydrin of 4-methylcyclohexanone, after conversion to the imino ester, afforded on pyrolysis a mixture of amides[12] which was not separated, but which on conversion to the oxazolidinedione could be separated readily into two products, form A, m.p. 107–108°, and form B, m.p. 76–79°. The stereochemistry of these forms was not further characterized, but each condensed readily with the three vinylpyridine compounds to yield the corresponding I derivatives.

**Pharmacology.**—The results have been collected in Table II.

Consideration of the response in the anticonvulsant test shows that the 4+ compounds (14, 17, 23, 25, 46, 47, 48, 49, 50) have, with the exception of compound 25, two small alkyl groups, or are derived from the spirostructure where the 5,5-substituent is 3-methylpentamethylene. The 3+ response is confined to alkyl structures, while none of the 5-phenyl substituted compounds showed interesting anticonvulsant activity. It is noteworthy that the series of compounds (46–51) derived from 4-methylcyclohexanone were considerably more effective than those derived from cyclohexanone (43–45) or cyclopentanone (40–42).

When the compounds with high anticonvulsant activity are related to the response in the Evipal sleeping test, it is noted that the majority also have a high response in this test. However, compounds 46–49 with high antimetrazole activity, reflected only little or no response in the Evipal test. Interestingly, in the 5,5-substituted 3-methylpentamethylene spiro series, use of the products derived from 4-vinylpyridine (compounds 50, 51) resulted in high anticonvulsant activity or decided prolongation of Evipal sleeping time, in contrast to products derived from 2-vinylpyridine and 2-vinyl-5-ethylpyridine (compounds 46–49).

The response in the Evipal test, in turn, did not necessarily correlate with anticonvulsant activity. Thus, the following structures (compounds 5, 20, 34, 36, 38) showed significant prolongation of Evipal sleeping time with little or no anticonvulsant activity (0 or 1+) being noted. Of this group only compound 36 is not derived from 4-vinylpyridine. In fact, an analysis of the findings shown in Table II indicates that the 3-(4-pyridylethyl) substituent on I is a requisite within this series (compounds 5, 17, 20, 23, 26, 29, 34, 38, 42, 45, 50, 51). When 3-(2-pyridylethyl)-substituted I showed decided prolongation of Evipal sleep time the corresponding 3-(4-pyridylethylated) derivative was equal or superior (see compounds 14 *vs.* 17; 18 *vs.* 20; 21 *vs.* 23).

(1) Presented at the 132nd Meeting of the American Chemical Society, New York, N. Y., September, 1957.

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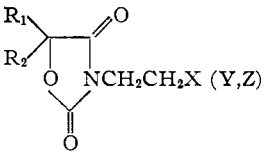
(10) R. W. Stoughton, THIS JOURNAL, **63**, 2376 (1941).

(11) V. H. Wallingford, M. A. Thorpe and R. W. Stoughton, *ibid.*, **67**, 522 (1945).

(12) B. Tchoubar, *Bull. soc. chim. France*, 160 (1949); *C. A.*, **44**, 4431 (1950), separated the mixture of the corresponding $\alpha$-hydroxy acids.

TABLE I: PYRIDYLETHYLATED OXAZOLIDINEDIONES



X = 2-pyridyl
Y = 5-ethyl-2-pyridyl
Z = 4-pyridyl

| Cmpd. | $R_1$ | $R_2$ | X, Y or Z | Salt[h] | M.p.,[i] or b.p., °C. (mm.) | Yield,[a] % | Formula | Analyses,[i] % Calcd. C | Calcd. H | Calcd. N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | H | H | X | | 89–90 | 71[b] | $C_{10}H_{10}N_2O_3$ | 58.3 | 4.9 | 13.6 | 58.1 | 4.9 | 13.9 |
| 2 | | | | $CH_3I$ | 168–173 | 53[d] | $C_{11}H_{13}IN_2O_3$ | | | 8.1 | | | 7.7 |
| 3 | H | H | Y | | 65 | 58[b] | $C_{12}H_{14}N_2O_3$ | 61.5 | 6.0 | 12.0 | 61.7 | 6.4 | 11.9 |
| 4 | | | | $CH_3I$ | 140–141 | 24[d] | $C_{13}H_{17}IN_2O_3$ | 41.5 | 4.6 | 7.5 | 41.7 | 4.9 | 7.3 |
| 5 | H | H | Z | | 128–129 | 41[e] | $C_{10}H_{10}N_2O_3$ | 58.3 | 4.9 | 13.6 | 58.3 | 5.0 | 13.8 |
| 6 | | | | $CH_3I$ | 143–145 | 21[d] | $C_{11}H_{13}IN_2O_3$ | 37.9 | 3.8 | 8.1 | 38.3 | 4.2 | 7.8 |
| 7 | $CH_3$ | H | X | | 126–130 (0.10) | 95 | $C_{11}H_{12}N_2O_3$ | | | | | | |
| 8 | | | | Picrate | 193–194 | 73[g] | $C_{17}H_{15}N_5O_{10}$ | 45.4 | 3.4 | | 45.7 | 3.4 | |
| 9 | $CH_3$ | H | Y | | 144–150 (0.01) | 71 | $C_{13}H_{16}N_2O_3$ | | | | | | |
| 10 | | | | Picrate | 163–164 | 71[g] | $C_{19}H_{19}N_5O_{10}$ | 47.8 | 4.0 | 14.7 | 48.1 | 3.9 | 14.9 |
| 11 | $CH_3$ | H | Z | | 131–148 (0.015) | 89 | $C_{11}H_{12}N_2O_3$ | | | | | | |
| 12 | | | | Picrate | 137–144 | 45[g] | $C_{17}H_{15}N_5O_{10}$ | 45.4 | 3.4 | 15.6 | 45.5 | 3.6 | 15.9 |
| 13 | | | | HCl | 174–175 | 66[d] | $C_{11}H_{13}ClN_2O_3$ | 51.5 | 5.1 | 10.9 | 51.7 | 5.0 | 10.6 |
| 14 | $CH_3$ | $CH_3$ | X | | 54–55 | 74[b] | $C_{12}H_{14}N_2O_3$ | 61.5 | 6.0 | 12.0 | 61.8 | 6.3 | 11.8 |
| | | | | | 115–132 (0.01) | | | | | | | | |
| 15 | $CH_3$ | $CH_3$ | Y | | 129–136 (0.01) | 86 | $C_{14}H_{18}N_2O_3$ | | | | | | |
| 16 | | | | Picrate | 177–179 | 71[g] | $C_{20}H_{21}N_5O_{10}$ | 48.9 | 4.3 | 14.3 | 48.9 | 4.5 | 13.8 |
| 17 | $CH_3$ | $CH_3$ | Z | | 73 | 50[b] | $C_{12}H_{14}N_2O_3$ | 61.5 | 6.0 | 12.0 | 61.8 | 6.0 | 11.6 |
| | | | | | 128–129 (0.04) | | | | | | | | |
| 18 | $C_2H_5$ | H | X | | 155 (0.05)[k] | 84 | $C_{12}H_{14}N_2O_3$ | 61.5 | 6.0 | 12.0 | 61.6 | 6.3 | 11.7 |
| 19 | $C_2H_5$ | H | Y | | 155 (0.08)[k] | 89 | $C_{14}H_{18}N_2O_3$ | 64.1 | 6.9 | 10.7 | 64.0 | 6.7 | 10.7 |
| 20 | $C_2H_5$ | H | Z | | 155 (0.01)[k] | 83 | $C_{12}H_{14}N_2O_3$ | 61.5 | 6.0 | 12.0 | 61.6 | 6.2 | 11.5 |
| 21 | $C_2H_5$ | $CH_3$ | X | | 144–162 (0.10)[k] | 90 | $C_{13}H_{16}N_2O_3$ | 62.9 | 6.5 | 11.3 | 63.1 | 6.6 | 10.8 |
| 22 | $C_2H_5$ | $CH_3$ | Y | | 142–170 (0.10)[k] | 90 | $C_{15}H_{20}N_2O_3$ | 65.2 | 7.3 | 10.1 | 64.7 | 7.2 | 9.8 |
| 23 | $C_2H_5$ | $CH_3$ | Z | | 80–81 | 70[f] | $C_{13}H_{16}N_2O_3$ | 62.9 | 6.5 | 11.3 | 63.0 | 6.7 | 11.2 |
| | | | | | 144–154 (0.10)[k] | | | | | | | | |
| 24 | $i$-$C_3H_7$ | H | X | | 160–170 (0.08)[k] | 85 | $C_{13}H_{16}N_2O_3$ | 62.9 | 6.5 | 11.3 | 63.4 | 6.7 | 10.9 |
| 25 | $i$-$C_3H_7$ | H | Y | | 162 (0.12)[k] | 85 | $C_{15}H_{20}N_2O_3$ | 65.2 | 7.3 | 10.1 | 65.8 | 7.5 | 9.7 |
| 26 | $i$-$C_3H_7$ | H | Z | | 164 (0.55)[k] | 80 | $C_{13}H_{16}N_2O_3$ | 62.9 | 6.5 | 11.3 | 63.1 | 6.8 | 11.3 |
| 27 | $C_6H_5$ | H | X | | 183–194 (0.06)[k] | | $C_{16}H_{14}N_2O_3$ | 68.1 | 5.0 | 9.9 | 67.9 | 5.0 | 9.7 |
| 28 | $C_6H_5$ | H | Y | | 39–43 | | $C_{18}H_{18}N_2O_3$ | 69.7 | 5.9 | 9.0 | 70.2 | 5.9 | 9.1 |
| 29 | $C_6H_5$ | H | Z | | 107–109 | 25 | $C_{16}H_{14}N_2O_3$ | 68.1 | 5.0 | 9.9 | 68.2 | 5.2 | 9.7 |
| 30 | $C_6H_5$ | $C_6H_5$ | X | | Residue | | $C_{22}H_{18}N_2O_3$ | | | | | | |
| 31 | | | | HCl | 154–170 | 70[d] | $C_{22}H_{19}ClN_2O_3$ | 66.9 | 4.9 | 7.1 | 67.3 | 4.8 | 6.8 |
| 32 | $C_6H_5$ | $C_6H_5$ | Y | | Residue | | $C_{24}H_{22}N_2O_3$ | | | | | | |
| 33 | | | | HCl | 145–156 | 64[d] | $C_{24}H_{23}ClN_2O_3$ | 68.2 | 5.5 | 6.6 | 68.1 | 5.4 | 6.9 |
| 34 | $C_6H_5$ | $C_6H_5$ | Z | | 107 | 65[b] | $C_{22}H_{18}N_2O_3$ | 73.7 | 5.1 | 7.8 | 73.2 | 5.1 | 7.9 |
| 35 | | | | $CH_3I$ | 166–168 | 47[e] | $C_{23}H_{21}IN_2O_3$ | 55.2 | 4.2 | 5.6 | 55.4 | 4.4 | 6.1 |
| 36 | $C_7H_{15}$[l] | H | X | | 166–174 (0.10)[k] | 85 | $C_{17}H_{24}N_2O_3$ | 67.1 | 8.0 | 9.2 | 67.0 | 8.1 | 8.8 |
| 37 | $C_7H_{15}$[l] | H | Y | | 170–172 (0.06)[k] | 85 | $C_{19}H_{28}N_2O_3$ | 68.6 | 8.5 | 8.4 | 68.7 | 8.2 | 8.2 |
| 38 | $C_7H_{15}$[l] | H | Z | | 167–172 (0.03)[k] | 85 | $C_{17}H_{24}N_2O_3$ | 67.1 | 8.0 | 9.2 | 66.7 | 8.0 | 9.0 |
| 39 | $-(CH_2)_4-$ | | X | | 162–176 (0.06)[k] | 85 | $C_{14}H_{16}N_2O_3$ | 64.6 | 6.2 | 10.8 | 64.8 | 6.3 | 10.7 |
| 40 | | | | Picrate | 188–191 | 75[g] | $C_{20}H_{19}N_5O_{10}$ | 49.1 | 3.9 | 14.3 | 49.2 | 3.9 | 13.8 |
| 41 | $-(CH_2)_4-$ | | Y | | 34–36 | 50[f] | $C_{15}H_{20}N_2O_3$ | 66.6 | 7.0 | 9.7 | 66.8 | 6.9 | 9.7 |
| 42 | $-(CH_2)_4-$ | | Z | | 77–78 | 64[f] | $C_{14}H_{16}N_2O_3$ | 64.6 | 6.2 | 10.8 | 64.7 | 6.3 | 11.0 |
| 43 | $-(CH_2)_5-$ | | X | | 63 | 78[f] | $C_{15}H_{18}N_2O_3$ | 65.7 | 6.6 | 10.2 | 65.7 | 6.9 | 10.3 |
| 44 | $-(CH_2)_5-$ | | Y | | 99–100 | 77[f] | $C_{17}H_{22}N_2O_3$ | 67.5 | 7.3 | 9.3 | 67.6 | 7.4 | 9.0 |
| 45 | $-(CH_2)_5-$ | | Z | | 108–109 | 71[b] | $C_{15}H_{18}N_2O_3$ | 65.7 | 6.6 | 10.2 | 65.9 | 6.9 | 9.8 |
| 46[m] | $-(CH_2)_2CHCH_3(CH_2)_2-$ | | X | | 60–61 | 75[f] | $C_{16}H_{20}N_2O_3$ | 66.6 | 7.0 | 9.7 | 66.8 | 6.9 | 10.4 |
| 47[n] | $-(CH_2)_2CHCH_3(CH_2)_2-$ | | X | | 110–120 | 35[f] | $C_{16}H_{20}N_2O_3$ | 66.6 | 7.0 | 9.7 | 66.9 | 6.9 | 9.6 |
| 48[m] | $-(CH_2)_2CHCH_3(CH_2)_2-$ | | Y | | 52–53 | 46[f] | $C_{13}H_{24}N_2O_3$ | 68.3 | 7.7 | 8.9 | 67.9 | 7.7 | 9.4 |
| 49[n] | $-(CH_2)_2CHCH_3(CH_2)_2-$ | | Y | | 45–65 | 65[f] | $C_{18}H_{24}N_2O_3$ | 68.3 | 7.7 | 8.9 | 68.3 | 7.6 | 9.0 |
| 50[m] | $-(CH_2)_2CHCH_3(CH_2)_2-$ | | Z | | 107–108 | 76[b] | $C_{16}H_{20}N_2O_3$ | 66.6 | 7.0 | 9.7 | 66.6 | 6.7 | 9.7 |
| 51[n] | $-(CH_2)_2CHCH_3(CH_2)_2-$ | | Z | | 84–87 | 69[f] | $C_{16}H_{20}N_2O_3$ | 66.6 | 7.0 | 9.7 | 66.9 | 6.9 | 9.9 |

[a] Recrystallizing solvents listed in footnotes *b* through *g*. [b] Ethyl acetate–hexane. [c] Ethyl acetate. [d] Ethyl acetate–alcohol. [e] Alcohol. [f] Hexane. [g] Water. [h] Unless otherwise indicated, compound is free base. [i] Melting points are not corrected. [j] Analyses by Weiler and Strauss, Oxford, England. [k] Isolated by short path distillation. [l] $C_7H_{15}$ corresponds to 3-heptyl. [m] From oxazolidinedione isomer, m.p. 107–108°. [n] From oxazolidinedione isomer, m.p. 76–79°.

TABLE II

PHARMACOLOGICAL SCREENING OF COMPOUNDS OF TABLE I

| Compd. | $LD_{min.}$[a] | Anti-convulsant[b] | Evipal time[c] | Depression of motor activity[d] |
|---|---|---|---|---|
| 1 | >1000 | 3+ | 0 | 0 |
| 3 | 1000 | 1+ | 0 | 15 |
| 5 | >1000 | 0 | 514 | 18 |
| 7 | >1000 | 3+ | .. | 0 |
| 9 | >1000 | 1+ | .. | 0 |
| 11 | >1000 | 0 | .. | 29* |
| 14 | 1000 | 4+ | 300 | 0 |
| 15 | >1000 | 1+ | .. | 0 |
| 17 | >1000 | 4+ | 630 | 25* |
| 18 | 1000 | 2+ | 300 | 0 |
| 19 | 1000 | 3+ | 100 | 0 |
| 20 | 750 | 0 | 300 | 0 |
| 21 | 750 | 2+ | 293 | .. |
| 22 | 1000 | 2+ | 191 | .. |
| 23 | 750 | 4+ | 1450 | 0 |
| 24 | 750 | 3+ | 29 | .. |
| 25 | >1000 | 4+ | 153 | .. |
| 26 | 500 | 2+ | 300 | 0 |
| 27 | >1000 | 1+ | 0 | 0 |
| 28 | >1000 | 1+ | 0 | 0 |
| 29 | 500 | 0 | 300[e] | 0 |
| 30 | 1000 | 0 | 0 | 35 |
| 32 | 1000 | 0 | 0 | 18 |
| 34 | >1000 | 0 | 300 | 23 |
| 36 | 1000 | 0 | 200 | 0 |
| 37 | >1000 | 0 | 0 | 0 |
| 38 | 400 | 1+ | 300 | 24 |
| 39 | 500 | 0 | 0 | 24 |
| 41 | >1000 | .. | 115 | 0 |
| 42 | 300 | 2+ | 333 | 0 |
| 43 | >1000 | 3+ | 0 | .. |
| 44 | 750 | 0 | .. | .. |
| 45 | 500 | 2+ | 570 | 0 |
| 46 | >1000 | 4+ | 87 | 0 |
| 47 | >1000 | 4+ | 0 | 0 |
| 48 | >1000 | 4+ | 67 | 0 |
| 49 | 1000 | 4+ | 0 | 0 |
| 50 | 750 | 4+ | 500 | 0 |
| 51 | 450 | 3+ | 742 | 0 |

[a] The $LD_{min.}$ was established subcutaneously in mice using 8–16 animals per test and is expressed as mg./kg. not toxic to any of the test animals. If the compound was not toxic at 1000 mg./kg., the response has been shown as >1000 without establishing the $LD_{min.}$ [b] The anticonvulsant response was established at one-half and one-fourth the $LD_{min.}$ subcutaneously in mice and evaluated in terms of protection afforded against metrazole seizures. A 4+ response indicates substantially complete protection when tested at one-fourth the $LD_{min.}$ Tridione ($LD_{min.}$ >1000 mg./kg.) used as a control drug showed a 4+ response. [c] Evipal sleeping time evaluated at one-third LD min. subcutaneously in mice. The average sleeping time of a control group of 6 mice was divided into average sleeping time of the group similarly treated plus test compound, multiplied by 100. Results reflect percentage increase in sleeping time. Meprobamate ($LD_{min.}$ 750 mg./kg.) tested in this manner gave 126% increase. [d] Compounds tested at 20 mg./kg. subcutaneously in rats. Compounds shown with asterisk were tested at 10 mg./kg.; see ref. 9 for procedure. Meprobamate under the conditions of this test was inactive at doses as high as 100 mg./kg. while Chlorpromazine ($LD_{min.}$ 400 mg./kg.) showed 71% decrease at 10 mg./kg. [e] Compound was toxic in this test.

Compound 23 is outstanding in this category in that the sleeping times were prolonged over 14 times that observed with the control group.

TABLE III

SUMMARY OF INITIAL REACTANTS

Xa = $R_1R_2C(OH)CN$, (cyanohydrin)
Xb = $R_1R_2C(OH)COOC_2H_5$, ($\alpha$-hydroxy ester)
Xc = $R_1R_2C(OH)CONH_2$, ($\alpha$-hydroxy amide)
Xd = (2,4-oxazolidinedione, II)

| $R_1$ | $R_2$ | X | M.p. or b.p., °C. (mm.) | Yield, % |
|---|---|---|---|---|
| H | H | Xd | 90–92[p] | 50[h] |
| $CH_3$ | H | Xd | 122 (2.0)[q] | 74[h] |
| $CH_3$ | $CH_3$ | Xd | 76–78[r] | 50 |
| $C_2H_5$ | H | Xa | 88 (12.0)[s] | 62 |
| $C_2H_5$ | H | Xc | 105–107[t] | 23[c] |
| $C_2H_5$ | H | Xd | 118 (0.7)[u] | 80 |
| $C_2H_5$ | $CH_3$ | Xa | 86 (12.0)[v] | 73 |
| $C_2H_5$ | $CH_3$ | Xc | 68–70[w,an] | 73[c] |
| $C_2H_5$ | $CH_3$ | Xd | 98 (0.005)[x] | 86 |
| $i$-$C_3H_7$ | H | Xa | 90 (10.0)[y] | 89 |
| $i$-$C_3H_7$ | H | Xc | 105–106[z] | 92[c] |
| $i$-$C_3H_7$ | H | Xd | 106–110 (0.1)[aa] | 84 |
| $C_6H_5$ | H | Xd | 108[ab] | 60[b] |
| $C_6H_5$ | $C_6H_5$ | Xb | 104–106 (4.0)[ac] | 43 |
| $C_6H_5$ | $C_6H_5$ | Xd | 135–136[ad] | 62[b] |
| $C_7H_{15}$[l] | H | Xb | 104–106 (4.0)[ae] | 32 |
| $C_7H_{15}$[l] | H | Xd | 124–130 (0.05)[af] | 66 |
| $-(CH_2)_4-$ | | Xa | 86 (0.7)[ag] | 77 |
| $-(CH_2)_4-$ | | Xc | 137–138[ah] | 69[c] |
| $-(CH_2)_5-$ | | Xa | 102 (3.0)[ai] | 72 |
| $-(CH_2)_5-$ | | Xc | 127–128[aj] | 39[c] |
| $-(CH_2)_5-$ | | Xd | 113–114[ak] | 75[g] |
| $-(CH_2)_2CHCH_3(CH_2)_2-$ | | Xa | 108 (7.0)[al] | 69 |
| $-(CH_2)_2CHCH_3(CH_2)_2-$ | | Xc | 145–150[am] | 86[b] |

[a–o] Have same significance as in Table I. [p] H. Aspelund, *Acta Acad. Aboensis, Math. et Phys.*, 11, No. 14 (1939); *C.A.* **33**, 6802 (1939), m.p. 89–90° (60%). [q] R. W. Stoughton, THIS JOURNAL, **63**, 2778 (1948), b.p. 147–148° (5.0 mm.) (81%). [r] Ref. *p*, m.p. 77°. [s] C. L. Stevens, E. Farkas and B. Gillis, THIS JOURNAL, **76**, 2697 (1954), b.p. 103–105° (20.0 mm.) (49%). [t] H. Bredereck, R. Gompper and G. Theilig, *Ber.*, **87**, 537 (1954), m.p. 105°. [u] Ref. *p*, m.p. 55–56°. [v] E. C. Chapin and R. F. Smith, THIS JOURNAL, **76**, 4179 (1954), b.p. 87–88° (17.0 mm.) (76%). [w] G. Ciamician and P. Silber, *Ber.*, **47**, 1814 (1914), m.p. 160°. [x] H. E. Erlenmeyer, A. Kleiber and A. Loebenstein, *Helv. Chim. Acta*, **21**, 1010 (1938), m.p. 31°. [y] A. Lipp, *Ann.*, **205**, 24 (1880), b.p. 106° (22.0 mm.). [z] A. Lipp, *Ann.*, **205**, 27 (1880), m.p. 104°. [aa] M. A. Spielman and G. M. Everett, THIS JOURNAL, **70**, 1021 (1948), b.p. 118–119° (1.5 mm.). [ab] H. Aspelund, *Finska Kemistsamfundets Medd.*, **49**, 42 (1940); *C.A.*, **35**, 3634 (1941), m.p. 108–109° (74%). [ac] H. Adkins and H. R. Billica, THIS JOURNAL, **70**, 3124 (1948), b.p. 138–140° (1.0 mm.) (51%). [ad] Ref. *q*, m.p. 135–136°. [ae] Not reported; used for preparing Xd derivative without analytical data. [af] Ref. 11, b.p. 144–146° (2.5 mm.) (78%). [ag] Ref. 12, b.p. 140° (40.0 mm.). [ah] R. Giuliano and G. Leonardi, *Farm. sci. e tec. (Pavia)*, **7**, 29 (1952); *C.A.*, **46**, 10113h (1952), m.p. 131°. [ai] Ref. 12, b.p. 129–131° (16.0 mm.). [aj] H. T. Bucherer and W. Brandt, *J. prakt. Chem.*, **140**, 129 (1934), m.p. 130°. [ak] A. Lespagnol, J. Mercier and J. Dupas, *Bull. soc. pharm. Lille*, **4**, 50 (1947); *C.A.*, **43**, 1406a (1949), m.p. 110°. [al] Ref. 12, b.p. 126–130° (12.0 mm.). [am] Mixture of two stereoisomers. *Anal.* Calcd. for $C_8H_{15}NO_2$. C, 61.1; H, 9.6; N, 8.9. Found: C, 61.3; H, 9.9; N, 8.8. [an] J. Verhulst, *Bull. soc. chim. Belges*, **39**, 563 (1930), reports m.p. 54–57°.

The depression of motor activity was manifested at very low dosages (10–20 mg./kg.) with these relatively non-toxic compounds, and depression was noted with compounds, 3, 5, 11, 17, 30, 32, 34, 38, 39. Of this group only compound 17 showed significant anticonvulsant activity, while in the Evipal sleeping time test compounds 3, 30, 32

and 39 were negative, and compounds 5, 17, 34 and 38 were active. In view of our prime interest in compounds which would function orally as depressors of motor activity, it was established that compound 11, the 5-methyl-3-(4-pyridylethyl)-oxazolidine-2,4-dione showed a 30% depression of motor activity when evaluated orally at 50 mg./kg.

## Experimental[13]

The many reactants prepared for this work which were not available commercially and which were previously described, have been gathered in Table III.

**3-Aza-1-oxaspiro[4,4]nonane-2,4-dione.**—A mixture of 3.6 g. (0.157 mole) of sodium metal in 38 ml. of methanol and 20.2 g. (0.172 mole) of diethyl carbonate was heated under reflux, a solution of 19.4 g. (0.15 mole) of 1-hydroxycyclopentane carboxamide in 50 ml. of hot methanol added, and heating continued for 4 hr. The methanol was removed and the residue was dissolved in 100 ml. of water and filtered. The filtrate was washed with two 50-ml. portions of ether and then aerated to remove the dissolved ether. After acidification with concentrated hydrochloric acid (13 ml.) and standing 16 hr., the product was separated, washed with water and dried, yielding 11.89 g., m.p. 132–133°. On extraction of the filtrate with four 50-ml. portions of ether, an additional 3.7 g., m.p. 132–133°, was obtained; total yield 67%.

*Anal.* Calcd. for $C_7H_9NO_3$: C, 54.2; H, 5.9; N, 9.0. Found: C, 54.4; H, 5.7; N, 8.7.

**3-Aza-1-oxaspiro-8-methyl[4,5]decane-2,4-dione** (2 Isomers).—The pair of stereoisomers was prepared as above from 18.5 g. (0.118 mole) of 1-hydroxy-4-methylcyclohexane carboxamide (mixture of isomers). In the final acidification step (careful addition of 3 *N* hydrochloric acid) the point of separation of the two isomers was taken as that point at which further acid addition gave a semi-permanent cloudiness which did not clear in a few seconds by crystallization to the hard needles of the high melting isomer. This isomer was filtered off, washed with water, and dried, yielding 9.9 g. (46%), m.p. 107–108° (form A), unchanged by recrystallization from ethyl acetate–hexane.

*Anal.* Calcd. for $C_9H_{13}NO_3$: C, 59.0; H, 7.2; N, 7.7. Found: C, 59.2; H, 7.1; N, 8.0.

On complete acidification of the filtrate, 3.2 g. (15%) of the low melting isomer was obtained, m.p. 76–79° (form B), unchanged by recrystallization from hexane.

*Anal.* Calcd. for $C_9H_{13}NO_3$: C, 59.0; H, 7.2; N, 7.7. Found: C, 59.4; H, 7.3; N, 7.8.

**Pyridylethylated Oxazolidinediones** (Compounds of Table I).—Equivalent amounts of the oxazolidinedione and the vinylpyridine were heated at 150° for 2 hr. If the residue solidified on cooling, it was triturated with hexane (in cases of compounds 41, 48 and 49, it was necessary to use *cold* hexane). The crude product was then dissolved in dilute hydrochloric acid, the solution washed with ether, and the product, precipitated on the addition of excess sodium bicarbonate solution, was filtered, washed with water, dried and recrystallized.

With compounds 29 and 34, the residue solidified on triturating with ether. Compound 29 was then worked up as above and compound 34 was recrystallized directly.

Compounds 1 and 3, water-soluble solids, were extracted from the aqueous solution with ether, the ether evaporated and the products recrystallized. Compound 5 was triturated with water, filtered, washed with water, dried and recrystallized.

Liquid residues were dissolved in dilute hydrochloric acid, the acid solutions washed with ether, the products extracted with benzene, the benzene evaporated and the products distilled under reduced pressures. In most cases where the boiling points anticipated would require a bath temperature high enough to reverse the reaction, purification was effected by short path distillation. In some cases (compounds 7, 11, 15, 30 and 32) the structures were characterized by the preparation of hydrochlorides or picrates.

Methiodides were prepared in the usual manner (compounds 2, 4, 6 and 35).

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YONKERS, NEW YORK

(13) Descriptive data shown in the tables are not reproduced in the Experimental section.

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[CONTRIBUTION FROM THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

# 10-(Dialkylaminoalkyl)-pyrido[3,2-b][1,4]benzothiazine (1-Azaphenothiazine) and Related Compounds

BY HARRY L. YALE AND FRANCIS SOWINSKI

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1-Azaphenothiazine has been prepared *via* the Smiles rearrangement of 2′-(3-nitro-2-pyridylthio)-acetanilide. 8-Chloro-1-azaphenothiazine was prepared similarly from 5′-chloro-2′-(3-nitropyridylthio)-acetanilide. Reaction between these two azaphenothiazine derivatives and various dialkylaminoalkyl chlorides in xylene, using sodamide as the condensing agent, led to a series of 10-dialkylaminoalkyl derivatives, which were converted to mono- and dihydrochlorides, as well as salts with oxalic acid.

In our studies with substituted phenothiazines[1,2] and the relation of their structure to pharmacological activity, we thought it of interest to synthesize pyrido[3,2-b][1,4]benzothiazine (1-azaphenothiazine) and 8-chloropyrido[3,2-b][1,4]benzothiazine (8-chloro-1-azaphenothiazine) and their 10-dialkylaminoalkyl derivatives. These compounds have shown interesting pharmacological properties and several are now undergoing clinical evaluation.

1-Azaphenothiazine and 8-chloro-1-azaphenothiazine are new compounds; a few mono- and diamino- and mono- and diamino-substituted 3- and 4-azaphenothiazines are known.[3,4]

The synthesis of 1-azaphenothiazine is outlined below and has, as its critical step, the Smiles rearrangement[5] of 2′-(3-nitro-2-pyridylthio)-acetanilide (I). Again, as reported in our previous paper[2] we prefer the rearrangement procedure involving the use of one equivalent of alkali in a mixture of acetone and ethanol; this makes possible the isolation of the intermediate 10-acetyl-1-azaphenothia-

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