TABLE I

TETRAALKYLAMMONIUM IODIDES $R_4N^+I^-$

No.[a]	R	Time, hr.	Solvent, ml.[b]	Millimoles Amine[c]	Millimoles RI	M.P., °	Yield, %	Formula	Analyses, % Nitrogen Calcd.	Nitrogen Found	Iodine Calcd.	Iodine Found
1A[d]	Hexyl	31	50	83	104	102–103	83	$C_{24}H_{52}NI$	2.91	2.89	26.35	26.10
2B	Heptyl	72	100	80	82	121–122	40	$C_{28}H_{60}NI$	2.61	2.51	23.60	23.80
3C	Octyl	96	200	84	271	127–128	30	$C_{32}H_{68}NI$	2.36	2.41 2.32	21.37	22.60 20.27
3D	Octyl	12	—	7.4	14.6	127–128	39	—	—	—	—	—
4A	Decyl	80	25	14	16	118–120	55	$C_{40}H_{84}NI$	1.98	1.98	17.98	17.71
4C	Decyl	48	200	85	280	118–120	38	—	—	—	—	—
5C	Dodecyl	96	200	65	200	116–117	38	$C_{48}H_{100}NI$	1.71	1.95	15.51	15.56
6C	Tetradecyl	96	100	80	339	114.5–115	36	$C_{56}H_{116}NI$	1.51	1.69	13.64	13.35
7E	Hexadecyl	96	50	29	17	110–111	15	$C_{64}H_{132}NI$	1.34	1.81	12.17	11.50

[a] Compounds 1 and 5 were recrystallized from ethanol-water; 4 from ethanol-water or ethyl acetate; 2 and 3 from ethyl acetate; 6 from ethanol; 7 from commercial absolute ethanol. [b] Reaction solvent for 1 and 6, ethanol; 2, 4A, and 4C, commercial absolute ethanol; 3C and 5, carbon dioxide-free commercial absolute ethanol; 7, benzene-ethanol 1:1. [c] Primary amines: 3C, 4C, 5C, 6C, and 7E. Tertiary amines: 1A, 2B, 3D, and 4A. [d] Letters refer to procedures.

alkyl iodide maintained at approximately 185°. The solid reaction mixture was first extracted with cold ether, followed by extraction with 100 ml. of boiling ether. On cooling the hot ether extract deposited 4 g. of crystalline solid; m.p. 79–80°. Girard and Forneau isolated a product melting at the same temperature which was claimed to be tetrahexadecylammonium iodide.

Evaporation of the combined cold ether extract and the filtrate from the hot ether extract gave 7.9 g. of crystalline residue; m.p. 42–43°. A mixture of 6.9 g. of this residue (0.029 mole, calculated on the basis of hexadecylamine; lit.,[7] m.p. 44–46°) and the alkyl iodide was refluxed in benzene-ethanol. After cooling, the resulting product was filtered and recrystallized.

A freshly prepared alcoholic paste of silver hydroxide was added to saturated ethanolic solutions of samples of the recrystallized product, tetrabutylammonium iodide, ditetradecylamine hydroiodide, and trioctylamine hydroiodide. The specific resistances increased on addition of the silver hydroxide by factors of 1.04, 1.18, 6.28, and 6.35, respectively. The two quaternary salts changed resistance only slightly, as there is no decrease in concentration of conducting species.

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(7) O. Westphal and D. Jerchal, *Ber.*, **73B**, 1002 (1940).

Pyridine-1-oxides. VI. Synthesis of Some 3-Styrylpyridine-1-oxides[1]

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During the course of an investigation of the chemistry of simple pyridine-1-oxides, it was found that 4-nitro-3-picoline-1-oxide condensed readily with benzaldehyde in ethanol or pyridine solution, in the presence of piperidine, to give 4-nitro-3-styrylpyridine-1-oxide.[2] Preliminary pharmacological screening of this compound indicated a high degree of antibacterial and antibiotic activity *in vitro*, and these findings prompted us to prepare a number of related 1-oxide derivatives.

4-Nitro-3-picoline-1-oxide was condensed with a number of other aromatic aldehydes, and the products formed are listed in Table I. All condensations could be carried out either in ethanol or in pyridine, with piperidine as catalyst. As pharmacological testing of many of these derivatives was difficult because of water insolubility, sodium salts of the phenolic derivatives were also prepared.

Treatment of 4-nitro-3-picoline-1-oxide with cinnamaldehyde, formaldehyde or glyoxal gave red, resinous materials, but no isolable products could be obtained. Attempts to condense 4-nitro-3-picoline-1-oxide with *p*-nitrosodimethylaniline failed.

Treatment of 4-nitro-3-styrylpyridine-1-oxide with acetyl chloride yielded 4-chloro-3-styrylpyridine-1-oxide. The action of thiourea in ethanol solution then gave the expected thiouronium salt, which on alkaline hydrolysis gave 4-mercapto-3-styrylpyridine-1-oxide along with a small amount of bis(1-oxy-3-styryl-4-pyridyl) sulfide.

It has already been pointed out by Jerchel and Heck[2] that neither 3-picoline, 4-nitro-3-picoline, nor 3-picoline-1-oxide gives a styryl derivative with benzaldehyde, and that both the 4-nitro and the 1-oxide groupings are therefore necessary for activation of the 3-methyl group. However, the 1-oxide grouping does effectively reduce electron density at the 3-position of the pyridine ring, as is clearly indicated by the observations that 3-amino-

(1) For the previous paper in this series, see E. C. Taylor and J. S. Driscoll, *J. Am. Chem. Soc.*, in press.

(2) Since this original observation was made (E. C. Taylor and A. J. Crovetti, Abstracts of Papers, 126th ACS Meeting, New York City, 1954, p. 24-N) the synthesis of 4-nitro-3-styrylpyridine-1-oxide has been reported (D. Jerchel and H. E. Heck, *Ann.*, **613**, 171 (1958)).

TABLE I

PRODUCTS FROM CONDENSATIONS OF 4-NITRO-3-PICOLINE-1-OXIDE AND AROMATIC ALDEHYDES

Compound No.	Ar	Reaction Time, Hr.	M.P., °	Recryst. solvent	Color	Yield, %	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
1	Phenyl	12	180–181	aq. DMF	Yellow-orange	73	$C_{13}H_{10}N_2O_3$	64.5	4.2	11.6	64.5	4.4	11.4
2	1-Naphthyl	8	254–255 dec.	aq. DMF	Orange	47	$C_{17}H_{13}N_2O_3$	69.9	4.1	9.6	69.9	4.3	9.8
3	4-Chlorophenyl	15	216–217	C_2H_5OH	Yellow	23	$C_{13}H_9ClN_2O_3$	56.4	3.3	10.1	56.7	3.2	9.8
4	4-Methoxyphenyl	16	196	aq. DMF	Orange	68	$C_{14}H_{12}N_2O_4$	61.8	4.4	10.3	61.9	4.3	10.4
5	2-Hydroxyphenyl	8	254 dec.	aq. DMF	Orange	47	$C_{13}H_{10}N_2O_4$	60.5	3.9	10.8	60.5	4.1	10.7
6	3,4-Methylenedioxyphenyl	11	238 dec.	aq. DMF	Orange	67	$C_{14}H_{10}N_2O_5$	58.8	3.5	9.8	59.1	3.4	9.5
7	3-Methoxy-4-hydroxyphenyl	4	237 dec.	aq. DMF	Red	27	$C_{14}H_{12}N_2O_5$	58.4	4.2	9.7	58.8	4.5	9.9
8	3,4-Dihydroxyphenyl	6	>360	aq. DMF	Red	11[a]	$C_{13}H_{10}N_2O_5$	56.9	3.7	10.2	57.1	3.5	10.3
9	4-Nitro-3-picoline-1-oxide												
10	4-Chloro-3-picoline-1-oxide												
11	4-Mercapto-3-styrylpyridine-1-oxide												
12	4-Chloro-3-styrylpyridine-1-oxide												

[a] Ethanol was used as solvent for the condensation. In all other cases, pyridine was used.

pyridine-1-oxide is a weaker base than 3-aminopyridine[3] and that 3-hydroxypyridine-1-oxide is a stronger acid than 3-hydroxypyridine.[4] 3-Aminopyridine-1-oxide fails to form an anil or an amide with acetoacetic ester, while 3-aminopyridine itself reacts readily.[3]

Compounds 1,2,4,6,9 and 11 (see Table I) showed some *in vitro* activity against *M. tuberculosis*. Compounds 1,2,4,7 and 8 were active *in vitro* against *Strep. pyogenes* C203. The inactivity of compound 3 against this microörganism indicates that 4-substituted 3-styrylpyridine-1-oxides are not uniformly active, and the low activity of compound 9 compared with a much higher activity of compound 1 points out the important activating influence of the styryl grouping. Slight *in vitro* activity was observed with compound 10 against *Pseud. aeruginosa*. Compound 6 was active *in vitro* against *Staph. aureus*. Slight amebiasis activity against *E. histolytics* was shown by compounds 1,2,3,4,6,7 (as the sodium salt), 9, 10, and 11. Unfortunately, none of the compounds tested showed sufficient *in vivo* activity to be of further interest.

EXPERIMENTAL[5]

Formation of styryl derivatives. The following procedures for the preparation of 4-nitro-3-styrylpyridine-1-oxide are illustrative of the methods used for all condensations of 4-nitro-3-picoline-1-oxide with aromatic aldehydes. Method A is similar to the previously published synthesis of 4-nitro-3-styrylpyridine-1-oxide.[2]

Method A. A mixture of 5.0 g. of 4-nitro-3-picoline-1-oxide,[6] 3.4 g. of purified benzaldehyde, 0.7 ml. of piperidine, and 15 ml. of absolute ethanol was heated under reflux for 3 hr. and then allowed to stand at room temperature for 8 hr. The resulting precipitate of yellow needles was collected by filtration, washed with ether, and recrystallized from ethanol to give 2.6 g. (47%, allowing for recovered starting material), of 4-nitro-3-styrylpyridine-1-oxide, m.p. 179–181°. This compound is reported to melt at 179–180°.[2] Concentration of both the ethereal and ethanolic filtrates gave 1.73 g. of crude starting material which, upon recrystallization from acetone, yielded 1.46 g. (29% recovery), m.p. 136–137°. This procedure was used successfully in runs of 25 g.

Method B. A mixture of 5.0 g. of 4-nitro-3-picoline-1-oxide, 10 ml. of reagent-grade pyridine, and 0.7 ml. of piperidine was heated on a steam bath for 12 hr. and then allowed to stand at room temperature for 12 hr. Filtration yielded 3.8 g. (73%, allowing for recovered starting material) of 4-nitro-3-styrylpyridine-1-oxide, m.p. 178–180°. Dilution of the filtrate with ether gave 1.7 g. of unchanged starting material. This procedure was also used successfully on runs of 25 g.

4-Chloro-3-styrylpyridine-1-oxide. A mixture of 12.0 g. of 4-nitro-3-styrylpyridine-1-oxide and 80 ml. of acetyl chloride was heated under reflux (hood) on a steam bath for 3 hr. The cooled reaction mixture was poured over ice with

(3) J. G. Murray and C. R. Hauser, *J. Org. Chem.*, 19, 2008 (1954).

(4) E. Shaw, *J. Am. Chem. Soc.*, **71**, 67 (1949).

(5) We are indebted for the microanalyses to Dr. Joseph F. Alicino, Metuchen, New Jersey. All melting points are uncorrected.

(6) E. C. Taylor and A. J. Crovetti, *J. Am. Chem. Soc.*, **78**, 214 (1956).

vigorous stirring and the mixture was brought to a volume of 2 l. by the addition of water. During the dilution white crystals of product separated. Filtration yielded 9.6 g. (84%) of almost colorless product, m.p. 161–163° dec. The colorless analytical sample, m.p. 167–168° dec., was prepared by recrystallization from aqueous ethanol with the use of charcoal.

Anal. Calcd. for $C_{13}H_{10}NO$: C, 67.4; H, 4.35; N, 6.05. Found: C, 67.7; H, 4.7; N, 5.9.

4-Mercapto-3-styrylpyridine-1-oxide. A mixture of 2.0 g. of 4-chloro-3-styrylpyridine-1-oxide, 0.6 g. of thiourea, and 20 ml. of ethanol was heated under reflux for 1.5 hr. The mixture was then chilled and filtered to give 1.71 g. (68%) of the thiouronium hydrochloride salt, m.p. 162° dec. This salt was suspended in 10 ml. of water and 5 ml. of cold 10% sodium hydroxide added with shaking. The mixture was filtered (yellow residue, 0.3 g., m.p. 200° dec.), the filtrate acidified with acetic acid and the precipitated solid collected by filtration to give 0.83 g. (62%, based on the thiouronium salt) of 4-mercapto-3-styrylpyridine-1-oxide, m.p. 145–146°.

Anal. Calcd. for $C_{13}H_{11}NOS$: C, 68.1; H, 4.8; N, 6.1. Found: C, 68.3; H, 4.6; N, 6.0.

Bis(1-oxy-3-styryl-4-pyridyl)sulfide. The yellow residue obtained above was purified by dissolution in boiling aqueous acetic acid and reprecipitation with ammonium hydroxide. The analytical sample m.p. 198–200° dec. was prepared by recrystallization from dimethylformamide.

Anal. Calcd. for $C_{26}H_{20}N_2O_2S$: C, 73.6; H, 4.8; N, 6.6. Found: C, 73.2; H, 4.7; N, 6.8.

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Pyrazolines[1]

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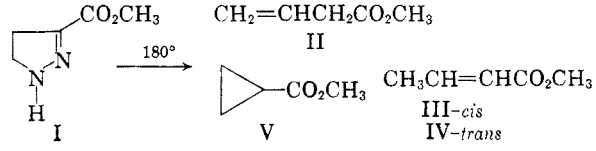
The pyrolysis of pyrazolines has long been regarded as a synthetic method for the preparation of derivatives of cyclopropane.[2] Particular use has been made of this method in the preparation of cyclopropanecarboxylic esters[3] and related compounds[4] where the pyrazoline is readily prepared by the addition of a diazoalkane to an α,β-unsaturated ester.

Of the methyl substituted 3-carbomethoxypyrazolines studied by von Auwers and Konig[3] only those which contained a methyl at the 3- position were found to give a cyclopropane product. A reinvestigation of this work which is now under way has shown that the products of pyrolysis of 3-carbomethoxypyrazolines are mixtures which contain in general α,β- and β,γ-unsaturated esters as well as the expected cyclopropanecarboxylic ester. A recent observation of the formation of a β,γ-unsaturated ketone from the pyrolysis of a pyrazoline in the steroid series has been reported.[5]

3-Carbomethoxypyrazoline (I), which was reported[3] to give in 81% yield methyl vinylacetate (II), has been shown to give a mixture in 80% yield of II, methyl *cis*-crotonate (III), methyl *trans*-crotonate (IV), and methyl cyclopropanecarboxylate in the ratio of 7:30:31:32, respectively.



Similarly methyl 2-methylcyclopropanecarboxylate has been isolated from the pyrolysis product from 4-methyl-3-carbomethoxypyrazoline and 5-methyl-3-carbomethoxypyrazoline in yields of 4 and 34%, respectively.[6]

That II, III, IV, and V were thermally stable under the reaction conditions was determined by heating each in a sealed tube for two hours at 195°. Not more than 2% rearrangement was observed. In the presence of iodine at 195° for five days, both II and IV gave an equilibrium mixture of the three olefins which contained 84% of IV, 12% of III, and 4% of II. These results would indicate that II and III are formed in the pyrolysis reaction by a kinetically controlled step and that although some isomerization may occur under the reaction conditions, it does not occur at a fast enough rate to give an equilibrium mixture.

It is hoped that by an extensive study of pyrazoline pyrolyses it will be possible to learn more about the mechanism[7] and the scope of the reaction as a synthetic method for the preparation of olefins and substituted cyclopropanes.

EXPERIMENTAL[8]

Pyrolysis of 3-carbomethoxypyrazoline (I). Thirteen g. of I (m.p. 65°, lit.[3] m.p. 66–68°) was placed in a 50-ml. round bottom flask fitted with a distilling head and heated in an oil bath. Pyrolysis began at 150° and was vigorous at 180°. The product distilled during pyrolysis and after 1 hr. 8 g. (80%) of a colorless liquid was collected.

Vapor chromatography of the product through a 10-ft. dinonyl phthalate column at 80° with a helium flow rate of 67 cc./min. gave four peaks at 20.8, 25.2, 32.4, and 36 min.

(1) Support for this work was received from the National Research Council of Canada and from the President's Committee on Research of the University of British Columbia.

(2) R. Huisgen, *Angew. Chem.*, **67**, 439 (1955).

(3) K. von Auwers and F. Konig, *Ann.*, **496**, 252 (1932).

(4) D. Gotkis and J. B. Cloke, *J. Am. Chem. Soc.*, **56**, 2710 (1934).

(5) H. L. Slates and N. L. Wender, *J. Am. Chem. Soc.*, **81**, 5472 (1959).

(6) Unpublished results from this laboratory.

(7) For proposals on the mechanism of this reaction see W. G. Young, L. J. Andrews, S. L. Lindenbaum, and S. J. Cristol, *J. Am. Chem. Soc.*, **66**, 810 (1944) and W. M. Jones, *J. Am. Chem. Soc.*, **81**, 3776 (1959).

(8) The instrument and columns for the vapor chromatograms were those available commercially under the trade name Aerograph.