persisted for 10 min. The mixture was acidified (sulfuric acid), and sodium bisulfite was added to dissolve the manganese dioxide. The suspension was extracted with ether; the ether was dried with sodium sulfate and evaporated at room temperature using a water aspirator. The residue was distilled using a falling film molecular still at 100° (0.01 mm.). The product was stored over copper wire in an evacuated (10^{-4} mm.) sealed off container for approximately 2 weeks. After this treatment the colorless oil could be handled in air for reasonable periods of time without darkening. The product was distilled:

Fraction	Wt. (G.)	n_D^{25}	B.P. (1.5 Mm.)
1	20	1.6295	Less than 105°
2	20	1.6596	105–110
3	70	1.6695	110–112
4	80	1.6709	112–113
5	70	1.6705	112–113

Attempts to distill the product prior to the treatment with copper wire led to extensive decomposition and the formation of black tar in the column.

Anal. Calcd. for $C_7H_8I_2$: C, 24.3; H, 2.3; I, 73.4; mol. wt., 346. Found: C, 24.8; H, 2.6; I, 72.9; mol. wt., 352, 354 (cryoscopic in benzene).

Diiodonortricyclene should be handled with caution; it appeared to be a powerful, though painless, blistering agent.

Diiodonortricyclene (1.00 g., 0.00289 mole) was reduced over prereduced platinum oxide in 75 ml. of 1*M* methanolic potassium hydroxide; 135 ml. (96% of 2 moles) of hydrogen was absorbed slowly at 25° and 1 atm. The suspension was filtered, and the filtrate was extracted with pentane. The pentane was washed with water, dilute sodium bisulfite solution, and water. After drying (sodium sulfate), the solution was distilled through a concentric rod column to yield nortricyclene, b.p. 108–110°; m.p. 55–56°. The infrared spectrum agreed with that of an authentic sample.

Reaction of diiodonortricyclene with magnesium, lithium, and phenyllithium. To a suspension of 1.41 g. (0.058 g.-atom) of magnesium in dry ether was added slowly 10.0 g. of diiodo compound (0.029 mole). After spontaneous reaction ceased, the mixture was refluxed for 30 min. Water was added to the mixture and the layers were separated. The ether layer was dried (sodium sulfate) and distilled to yield 2 g. (75%) of bicycloheptadiene, b.p. 88–90°. The bicycloheptadiene was identified by retention time on a silicone rubber column and by comparison of its infrared spectrum with that of an authentic sample. From the original hydrolysis mixture 0.80 g. of magnesium metal (56%) was recovered.

The reaction of 0.42 g. of lithium wire in ether with 10 g. of diiodonortricyclene gave 1.90 g. (70%) of bicycloheptadiene. Phenyllithium (0.06 mole) and 10.0 g. of diiodo compound likewise yielded 1.95 g. of bicycloheptadiene (73%). Iodobenzene was present in the distillation residue (infrared spectrum of vapor phase chromatography fraction).

Reaction of dibromonortricyclene with magnesium and lithium. Dibromonortricyclene (b.p. 72–75° (1.7 mm.); n_D^{25} 1.5770) was prepared from bicycloheptadiene and bromine in carbon tetrachloride[5,6,8]; olefins were removed with permanganate. A solution of 10.0 g. of dibromonortricyclene in ether was allowed to react with 1.93 g. of magnesium. When the reaction ceased, the suspension was refluxed for 20 min. Water was added (a precipitate formed which dissolved on the addition of more water), and the layers were separated. The ether layer was dried (sodium sulfate) and distilled to yield 1.8 g. of bicycloheptadiene (49%). The use of lithium wire in ether gave 45% bicycloheptadiene from dibromonortricyclene. The infrared spectra of the samples of bicycloheptadiene were identical with that of an authentic sample.

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S-Alkoxymethyl and *S*-Alkylmercaptomethyl Derivatives of 2-Pyridinethiol 1-Oxide

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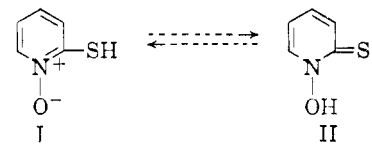
Received March 15, 1961

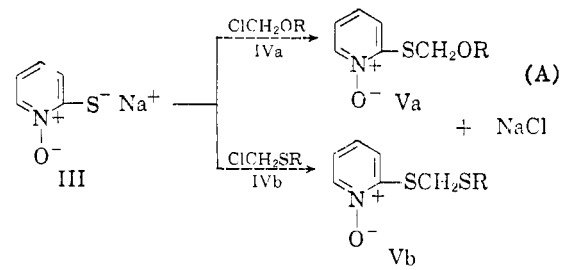
2-Pyridinethiol 1-oxide (I), (also known as 1-hydroxypyridine-2-thione from its tautomeric form, II) has demonstrated strong bactericidal and fungi-



I II

cidal properties,[2] as have a number of its derivatives.[3a] In the process of studying some of the physical and biocidal properties of this interesting structure, we have synthesized a series of previously unreported alkoxymethyl (Va) and alkylmercaptomethyl derivatives (Vb).[3b]

Method. Two general procedures were used. The first method involved the reaction of the sodium salt of 2-pyridinethiol 1-oxide, III, with a chloromethyl alkyl ether (IVa) or thio ether (IVb) as in reaction (A). Inert solvents were used.



III Va Vb (A)

Dioxane was first tried because of its fair solvent power on the sodium salt (III). It was later abandoned because its low volatility and tenacity for water caused difficulties in the purification and crystallization of the products. Acetone or 1,2-dimethoxyethane were found to work well. Although the sodium mercaptide (III) was only

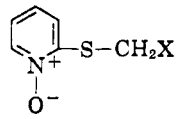
(1) Present address: Metal and Thermit Corp., Research Laboratories, Rahway, N. J., to whom requests for reprints should be sent.

(2) E. Shaw, J. Bernstein, K. Losee, and W. Lott, *J. Am. Chem. Soc.*, 72, 4362 (1950).

(3a) U. S. Patents; 2,686,786; 2,734,903; 2,742,393; 2,742,476; 2,745,826; 2,678,116; 2,809,971; 2,826,585; 2,826,586; 2,922,790; 2,922,791; 2,922,792; 2,922,793; 2,940,978. (3b) U. S. Patent 2,932,647 to Jack Rockett (Olin Mathieson Chemical Corp.).

TABLE I

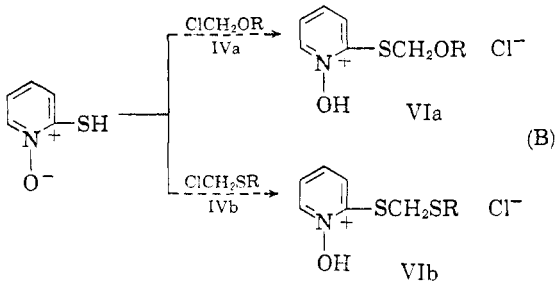
2-ALKOXYMETHYLMERCAPTOPYRIDINE 1-OXIDES AND 2-ALKYLMERCAPTOMETHYLMERCAPTOPYRIDINE 1-OXIDES



	Crude Yield, %	Recrystallized M.P.	Sulfur, % Calcd.	Sulfur, % Found	Other Elements, % Calcd.	Other Elements, % Found
$OCH_3 \cdot HCl$	100	129.5–135	—	—	—	—
OCH_2CH_3	69	69.5–72	17.31	17.34	—	—
$OCH_2CH_2CH_3$	65	80.5–83.5	16.13	16.73	C 54.3 H 6.6	54.6 6.6
$OCH(CH_3)_2 \cdot HCl$	80	101.5–105.5	13.60	13.69	—	—
O"isooctyl" $\cdot HCl$	80	75–76	10.52	10.56	—	—
$O(CH_2)_{11}CH_3$	87.5	78–79.5	9.84	10.31	—	—
$O(CH_2)_{17}CH_3$	63	90–93	8.11	8.14	—	—
SCH_3	63	105–107	34.24	34.08	—	—
$SCH_2CH_2CH_3 \cdot HCl$	69	98.5–100.5	25.45	24.32	N 5.56	5.29

slightly soluble in these solvents, the reaction proceeded at a satisfactory rate around 60°. Insoluble sodium chloride, which formed in the reaction, was filtered. The solvent was evaporated and the product purified by recrystallization. In some cases where the desired products could not be obtained as solids, they were isolated as their hydrochlorides, (VI), by the addition of dry hydrogen chloride to benzene solutions of the crude oils.

The second procedure (B) involved reaction of 2-pyridinethiol 1-oxide (I) with the desired chloromethyl alkyl ether (IVa) or thio ether (IVb) in benzene. The hydrochloride of the desired product, VI, precipitated and could be obtained in air yield and in good purity. Crude yields of 63–88% were

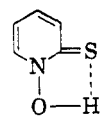


(B)

obtained by either procedure (see Table I). Wherever the intermediate alkyl chloromethyl ether or thio ether was unavailable commercially, it was prepared by the reaction of formaldehyde, dry hydrogen chloride, and the alcohol or mercaptan containing the desired alkyl group.

The various alkoxymethyl and alkylmercaptomethyl derivatives are described in Table I.

Structure of the products. 2-Pyridinethiol 1-oxide can be considered to be a tautomeric mixture of forms I and II. The thione form is preferred by E. Shaw *et al.*,[2] but Katritzky and Jones[4b] favor a form in which the hydrogen is bonded between the sulfur and the oxygen (VII). A strong band at 11.90–11.92 μ, common to the infrared spectra of



VII

both pyridine 1-oxide and 2-pyridinethiol 1-oxide, causes us to favor the *N*-oxide form (I). The same strong band is found in the infrared spectrum of the propoxymethyl derivative (Va, R = C_3H_7). We associate this band with the pyridine *N*-oxide structure, because, on formation of the hydrochloride, *e.g.*, VIa, R = C_3H_7, the 11.92 9 band disappears. This leads us to the conclusion that our alkylations took place at the sulfur atom. This conclusion is in agreement with the *S*-alkylation of II with 2-vinylpyridine postulated by Cislak,[5] and the *S*-alkylation of II with 2-bromopyridine 1-oxide as formulated by Bernstein,[6] and with the structure of the benzyl derivative (Va, R = $CH_2C_6H_5$) as assigned by Jones and Katritzky.[4b]

Hydrolysis of the products. The 2-alkoxymethyl mercaptopyridine 1-oxides and the 2-alkylmercaptomethylmercaptopyridine 1-oxides are formals, and thus subject to acid hydrolysis. 2-Pyridinethiol 1-oxide, formaldehyde, and an alcohol are regenerated in the process. The rates of hydrolysis could be conveniently studied at 30°. For the *n*-propoxy derivative (Va, R = C_3H_7) hydrolysis was negligible at *p*H 3, but increased with increased acidity of the solution as shown in Table II. The longer the chain in the alkoxy group (Va), the slower the hydrolysis. The following order of increasing stability to hydrolysis was found at 30°

(4)(a) A. R. Katritzky and R. A. Jones, *J. Chem. Soc.*, 2947 (1960). (b) R. A. Jones and A. R. Katritzky, *J. Chem. Soc.*, 2937 (1960).

(5) F. E. Cislak, U. S. Patent 2,826,585 (1958).

(6) J. Bernstein, E. R. Squibb Division, Olin Mathieson Chemical Corp., New Brunswick, N. J., private communication.

TABLE II

HYDROLYSIS OF 2-PROPOXYMETHYLMERCAPTOPYRIDINE 1-OXIDE AT 30°

pH	% Hydrolyzed[a]	
	5 Hours	75 Hours
5.2	0	<3.5
4.1	0	<9.5
3.1	<0.5	4.0
2.2	5.0	19.0
1.3	25.0	65.0
−0.6	91.0	87[b]

[a] Determined as pyridinethione by colorimetric analysis of complex with ferric chloride. [b] Low figure probably due to further decomposition of pyridinethione in strong acid medium.

and *p*H of 2.2: isopropoxy < ethoxy < propoxy < "isooctyloxy" < dodecyloxy < octadecyloxy.[7]

The alkylmercaptomethyl derivatives (Vb) were very resistant to hydrolysis. Thus, the propylmercaptomethyl compound (Vb, R = C_3H_7) showed only 3.5% hydrolysis in 4*N* acid at 30° after forty-one hours.

EXPERIMENTAL

Chloromethylalkyl ethers (IVa) *and sulfides* (IVb). Methyl chloromethyl ether was obtained from Matheson, Coleman and Bell and methyl chloromethyl sulfide was obtained from Stauffer Chemical Corp. The remaining chloromethyl ethers and sulfides were prepared by methods summarized by Walker.[8]

Alkylation of 2-pyridinethiol 1-oxide. Reaction A. By use of the sodium salt (III). The sodium salt of 2-pyridinethiol 1-oxide (0.05–0.50 mole) was slurried in acetone (1,4-dioxane and 1,2-dimethoxyethane were also used successfully) using 200–300 ml. of solvent per 0.1 mole. While stirring, an equimolar quantity of the appropriate alkylchloromethyl ether or sulfide was added slowly. The mixture was then refluxed for 1 to 2.5 hr. and cooled. Sodium chloride was then filtered off, and the solvent evaporated under vacuum. (For the less soluble products, a hot filtration was required.) The products were isolated as oils which generally crystallized upon cooling. They were then purified by recrystallization in or extraction with hydrocarbon solvents or isopropyl ether. The ethoxy, *n*-propoxy, dodecyloxy, octadecyloxy, and methylmercapto derivatives were prepared by this procedure. Yields, melting points, and analyses are given in Table I.

Reaction B. By use of the free acid (I). 2-Pyridinethiol 1-oxide (0.25–0.4 mole) was dissolved in 250–400 ml. of dry benzene. An equimolar quantity of the appropriate alkylchloromethyl ether or mercaptan was slowly added while stirring. The solution was then heated to 61–62° for 1.5 to 3 hr. After cooling the crystalline hydrochloride product was washed with benzene and dried. Recrystallization was effected from acetone and from a 1:1 mixed solvent of hexane and methylene chloride. The methoxy, isopropoxy, "isooctyloxy", and propylmercapto derivatives were prepared by this procedure. Yields, melting points, and analyses are given in Table I.

(7) B. A. Starrs, Olin Mathieson Chemical Corp., New Haven, private communication.

(8) J. F. Walker, *Formaldehyde*, 2nd ed., Reinhold Publishing Co., New York, 1953, pp. 212–216.

Acknowledgment. We wish to express our appreciation to Mr. Bernard A. Starrs for his hydrolysis studies of our compounds, and to Mr. Herbert G. Nadeau for his aid in interpreting our infrared spectra.

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Some Basically Substituted Acrylic Acid Derivatives

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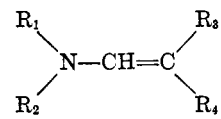
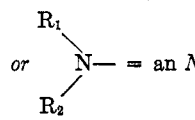
Received March 15, 1961

A number of basically substituted, unsaturated compounds have stimulant effects on the central nervous system. Included in this group are: arecoline,[2] lysergic acid derivatives (such as LSD-25[3] and LAE-32[4]), 1.4-bis(1-pyrrolidyl)-2-butyne,[5] β-amino-acroleins,[6,7] and nalorphine.[8] It was decided to probe the area of basically substituted acrylic acid derivatives, exemplified by I, for such activity. Varying, but definite, central stimulant effects were found in the series. Evidence of cardiovascular-renal actions and a suggestion of anti-inflammatory effects were also uncovered. Unfortunately, the potency was not at a practical level of utility in any instance.



I

R_1 = H and R_2 = alkyl, aralkyl, or heteryl group



or R_1R_2N— = an *N*-heteryl moiety

R_3 = H, CN, $COOC_2H_5$
R_4 = CN, $COOC_2H_5$

The greater number of compounds were of a basically substituted α-carbethoxy acrylic ester type (I, with R_3 = R_4 = $CO_2C_2H_5$). These were

(1) Present address: Nalco Chemical Co., Chicago 38, Ill.

(2) L. Small, *Organic Chemistry, an Advanced Treatise*, Vol. 2, H. Gilman, Ed., J. Wiley and Sons, Inc., New York, 2nd ed., 1943, p. 1184.

(3) E. Rothlin, *J. Pharm. Pharmacol.*, **9**, 569 (1957).

(4) H. Solms, *Schweiz. Arch. Neurol. Psychiat.*, **73**, 440 (1954).

(5) G. M. Everett, L. E. Blockus, and I. M. Shepperd, *Science*, **124**, 79 (1956).

(6) F. Zinnitz and K. Heuwing, *Arch. exp. Pathol. Pharmacol.*, **213**, 59 (1951).

(7) F. Zinnitz, F. Wille, and G. Huber, *Pharmazie*, **12**, 13 (1957).

(8) L. A. Woods, *Pharmacol. Revs.*, **8**, 175 (1955).