TABLE I

ULTRAVIOLET SPECTRA AND ACID DISSOCIATION CONSTANTS

| Compds | pH 1 λmax, mμ | pH 1 ε | Distd $H_2O$ λmax, mμ | Distd $H_2O$ ε | pH 11 λmax, mμ | pH 11 ε | Methanol λmax, mμ | Methanol ε | $pK_a$ |
|---|---|---|---|---|---|---|---|---|---|
| 6-Thioguanine[a] | 258 | 8100 | | | 242 | 8700 | | | 8.2 |
| | 347 | 20900 | | | 270 | 7200 | | | |
| | | | | | 322 | 16000 | | | |
| 6-Methylthioguanine[b] | 241 | 7000 | | | 228 | 20200 | | | |
| | 273 | 10000 | | | 313 | 10600 | | | |
| | 317 | 13000 | | | | | | | |
| 6-Selenoguanine[c] | 263 | 5600 | 360 | 10800 | 318 | 6900 | | | 7.81,7.62[d] |
| | 372 | 16500 | | | | | | | |
| 6-Methylselenoguanine | 329 | 12700 | 246 | 8900 | 317 | 12300 | | | |
| | | | 315 | 12400 | | | | | |
| | pH 4–6 | | | | | | | | |
| 6-Thioguanosine[e] | 257 | 8800 | | | 252 | 14700 | | | 8.33 |
| | 342 | 24800 | | | 319 | 21000 | | | |
| 6-Selenoguanosine | 267 | 4600 | 264 | 5600 | 256 | 10800 | | | |
| | 365 | 18200 | 357 | 22300 | 330 | 17200 | | | |
| 6-Methylthioguanosine[f] | | | | | | | 221 | 15300 | |
| | | | | | | | 245 | 14400 | |
| | | | | | | | 310 | 11000 | |
| 6-Methylselenoguanosine | | | 252 | 9700 | | | 221 | 12900 | |
| | | | 316 | 13100 | | | 252 | 10000 | |
| | | | | | | | 314 | 10100 | |
| 6-Selenoinosine[g] | | | 235 | 7700 | | | | | |
| | | | 345 | 11200 | (Phosphate–citrate buffer, pH 7) | | | | |
| 6-Methylselenoinosine | | | 229 | 8400 | | | 230 | 8000 | |
| | | | 302 | 13500 | | | 300 | 17600 | |

[a] G. B. Elion and G. Hitchings, *J. Amer. Chem. Soc.*, **77**, 1676 (1957). [b] J. A. Montgomery and L. B. Holum, *ibid.*, **79**, 2185 (1957). [c] See ref 2. [d] A. F. Ross, private communication (it was determined by a spectrophotometric method). [e] J. J. Fox, I. Wempen, A. Hampton, and I. L. Doerr, *J. Amer. Chem. Soc.*, **80**, 1669 (1958). [f] C. W. Noell and R. K. Robins, *J. Med. Pharm. Chem.*, **5**, 1074 (1962). [g] See ref 7.

TABLE II

EFFECT OF 6-THIOGUANINE, SELENOGUANINE, SELENOGUANOSINE, METHYLSELENOGUANINE, AND METHYLSELENOGUANOSINE ON THE GROWTH OF L-5178Y

| Control 100% | % survival $1.0 \times 10^{-4}$ M | % survival $1.0 \times 10^{-5}$ M | % survival $1.0 \times 10^{-6}$ M |
|---|---|---|---|
| Thioguanine | 4 | 9 | 33 |
| Selenoguanosine | 4 | 8 | 31 |
| Selenoguanine | 12 | 20 | 45 |
| Methylselenoguanosine | 21 | 46 | 80 |
| Methylselenoguanine | 24 | 45 | 82 |

$H_2O$ and then cooled to room temp. All determinations were made in duplicate.

**Stability Studies.**—The half-life from the height of the 360-mμ peak of **1** in $H_2O$ (pH 6.01) at room temp was about 24 hr, in phosphate buffer at pH 7.0 2.5 hr (as compared with 7 hr for selenoguanine). Methylselenoguanine and methylselenoguanosine were stable in both conditions. Because of the demonstrated instability of 6-selenoguanine and 6-selenoguanosine, fresh solns of these two compds were prepared for biological studies.

**Biological Testing.** (1) **Tissue Culture Study.**—The results of the cell culture using the L-5178Y cell are shown in Table II. The cell viability was determined by the dil agar colony method.[8] Thioguanine, Se-guanine, Se-guanosine, and their derivatives inhibited cell division and caused cell death over a concn range from $1.0 \times 10^{-4}$ mole to $1.0 \times 10^{-6}$ mole after 2 hr incubation. 6-Selenoguanosine was found to have activity approx equal to thioguanine. Methylseleno derivatives were less active than thioguanine at lower dosage. It is of interest that selenoguanosine is more soluble than selenoguanine or thioguanine. This may increase its application.

(2) **Enzyme Study.**—Ross and Parks[9] found that selenoguanine was converted to selenoguanosine by a highly purified enzyme (PNP) isolated from human red blood cells. However, the guanase isolated from S-180 cells does not react with selenoguanine. Details will be published elsewhere.

**Acknowledgment.**—The author is indebted to Miss Andrea Gorske for obtaining the spectroscopic and potentiometric data, to Drs. G. Fischer and M. Y. Wang Chu for carrying out the biological tests, and to Drs. R. E. Parks, Jr., and P. Calabresi for their encouragement during the course of this investigation.

(8) M. Y. Chu and G. A. Fischer, *Biochem. Pharmacol.*, **17**, 753 (1968).
(9) A. F. Ross and R. E. Parks, Jr., unpublished data.

## Amebicides. *l*-Emetine Derivatives

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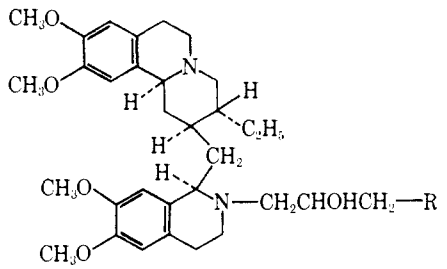
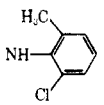
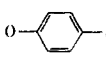
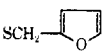
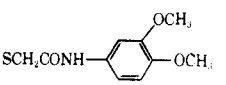
Some *N*-hydroxyalkyl derivatives of *l*-emetine have a greater amebicidal activity and a lower toxicity than the parent compound.[1,2] We have now synthetized some N-derivatives by the reaction of *l*-emetine with 1-alkyloxy-, 1-alkylthio-, 1-dialkylamino-2,3-epoxypropane (see Table I). The compounds have been evaluated for their acute toxicity ($LD_{50}$), for their activity against *E. histolytica*,[3] and Ehrlich carcinoma.[4] Com-

(1) D. E. Clark, R. F. K. Meredith, A. C. Ritchie, and T. Walker, *J. Chem. Soc.*, 2490 (1962).
(2) A. C. Ritchie, D. R. Preston, T. Walker, and K. D. Whithing, *ibid.*, 3385 (1962).
(3) J. E. Linch, B. J. Banforth, and D. Goeckeritz, *Antibiot. Chemother.*, **6**, 330 (1956).
(4) J. S. Evans, G. D. Mengel, J. Cern, and R. L. Johnston, *Antibiot. Annu.*, **1958–1959**, 565 (1960).

TABLE I



| No. | R | Heating time, day (yield) | Mp, °C (sint to °C) | $[\alpha]^{26}D$,[a] degrees | $R_E$[b] | Formula[c] | $LD_{50}$, mg/kg iv | % inhib, Ehrlich ascites carcinoma | *In vitro* activity against *E. histolytica* MIC, μg/ml |
|---|---|---|---|---|---|---|---|---|---|
| 1 | H | 7 (67) | 205–207 (180) | −3 | 1.40 | $C_{32}H_{46}N_2O_5 \cdot 2HCl \cdot C_3H_8O$ | 35 | Inactive | 200 |
| 2 | $CH_3$ | 3 (37) | 218–220 (192) | −27 | 1.83 | $C_{33}H_{48}N_2O_5 \cdot 2HCl$ | 51 | Inactive | 100 |
| 3 | $N[(CH_2)_4CH_3]_2$ | 3 (56) | 213–216 (183) | +44 | 0.75 | $C_{42}H_{67}N_3O_5 \cdot 3HCl$ | 31 | 45 | 100 |
| 4 | $NC_5H_{10}$ | 1.5 (52) | 244–248 (204) | +44 | 0.63 | $C_{37}H_{55}N_3O_5 \cdot 3HCl \cdot 0.5C_3H_8O$ | 37 | 20 | 40 |
| 5 | $NC_4H_8O$ | 2 (34) | 223–225 (190) | +36 | 0.65 | $C_{36}H_{53}N_3O_6 \cdot 3HCl$ | 28 | 60 | 40 |
| 6 |  | *d* (21) | 228–232 (*d*) | +4 | 0.65 | $C_{37}H_{57}N_4O_5 \cdot 4HCl$ | 25 | | 100 |
| 7 |  | *d* (33) | 238–240 (215) | +66 | 0.86 | $C_{40}H_{55}ClN_3O_5 \cdot 3HCl$ | 17.5 | 80 | 40 |
| 8 | $OC_2H_5$ | 8 (20) | 190–192 (178) | −30 | 1.42 | $C_{34}H_{50}N_2O_6 \cdot 2HCl$ | 20 | Inactive | 40 |
| 9 | $O(CH_2)_6CH_3$ | 9 (55) | 128–130 (87) | −8 | 0.88 | $C_{40}H_{60}N_2O_6 \cdot 2HCl \cdot C_3H_8O$ | 27 | Inactive | 20 |
| 10[e] | $OCH_2CH(C_2H_5)(CH_2)_3CH_3$ | 3 (39) | 165–168 (130) | −20 | 1.75 | $C_{40}H_{62}N_2O_6 \cdot 2HCl$ | 31.5 | Inactive | 40 |
| 11 |  | 2 (28) | 170–173 (151) | −14 | 1.78 | $C_{39}H_{51}N_2O_7 \cdot 2HCl$ | 9 | Inactive | 40 |
| 12 |  | 4 (59) | 168–172 (157) | −5 | 1.79 | $C_{39}H_{52}N_2O_6S \cdot 2HCl$[f] | 34 | 20 | 100 |
| 13 | $SCH(CH_3)C_2H_5$ | 1.5 (32) | 190–194 (172) | −45 | 1.78 | $C_{36}H_{54}N_2O_5S \cdot 2HCl \cdot 3H_2O$[f] | 83.5 | 20 | 40 |
| 14 | $SC(CH_3)_3$ | 2 (42) | 182–184 (152) | −28 | 1.91 | $C_{36}H_{54}N_2O_5S \cdot 2HCl$[f] | 82.5 | 10 | 100 |
| 15 | $SCH_2C_6H_5$ | *d* (24) | 171–175 (153) | −15 | 2.03 | $C_{39}H_{52}N_2O_5S \cdot 2HCl$[f] | 45 | Inactive | 40 |
| 16 |  | 2 (19) | 158–162 (123) | −9 | 1.76 | $C_{37}H_{50}N_2O_6S \cdot 2HCl \cdot 0.66C_3H_8O$[f] | 54 | Inactive | 40 |
| 17 |  | 1 (20) | 203–204 (135) | −11 | 0.84 | $C_{42}H_{56}N_3O_8S \cdot 2HCl$[f] | 25 | 23 | 200 |
| | *l*-Emetine | | | | | $C_{29}H_{40}N_2O_4 \cdot 2HCl \cdot 5H_2O$ | 15.1 | 55 | 10–20 |

[a] $CHCl_3$ (*c* 1). [b] Compd gave a single spot on tlc with Stahl silica gel $HF_{254}$ ($R_E$ = relative mobility on tlc moistened with $CHCl_3$–MeOH (85:15) with *l*-emetine as unity). [c] Analytical results obtained for C, H, Cl, N were within ±0.4% of theoretical values. [d] 8 hr at 100° under $N_2$. [e] The biochemical determination of cardiotoxicity according to Appelt and Heim[5] *J. Pharm. Sci.*, **57**, 1428 (1968); shows that *l*-emetine decreases the oxydation rate on the pyruvates (19%) and lactates (20%) to a greater extent than **10** (11 and 6%, respectively). [f] Also analyzed for S.

pound **10** has also been subjected to biochemical determination of cardiotoxicity according to Appelt and Heim.[5]

## Experimental Section

**Preparation and Characterization of Compounds.**—Most of the compounds were prepared by condensation in EtOH of an appropriate epoxide (0.04 mole) with *l*-emetine·2HCl (0.01 mole) at 37° for 1–9 days. The oily residue obtd by evapg the solvent was taken up in dil HCl. The filtered acid soln was neutralized potentiometrically and extd with $Et_2O$. The combined exts were dried and acidified with HCl–*i*-PrOH. The cryst hydrochlorides were filtered, dried, analyzed, and chromatographed. The purification procedure had to be repeated until pure products were obtained. Melting points were taken with a Tottoli apparatus and are uncorrected.

(5) G. D. Appelt and H. C. Heim, *J. Pharm. Sci.*, **57**, 1428 (1968).