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Carcinostatic Methanesulfonic Acid Esters of Nitrogen Mustard Analogs

In the course of our study on carcinostatic substances, four sulfonic esters of nitrogen mustard analogs were synthesized and their biological activity against *Yoshida sarcoma* was evaluated.

The compounds were synthesized following the procedure of Sprague, *et al.*[1] By the reaction with methanesulfonic anhydride in acetonitrile, 2,2'-dihydroxy-N-methyldiethylamine yielded 2,2'-dimesyloxy-N-methyldiethylamine (No. 839) isolated as its

Table I.

Compound No.	Formula	*in vivo* LD$_{50}$ (mg./kg.)	*in vivo* MTD[a] (mg./kg.)	*in vivo* MED[b] (mg./kg.)	*in vivo* CI[c] (LD$_{50}$/MED)	*in vivo* MEC[d] (mM)
839	$CH_3-N(CH_2CH_2OSO_2CH_3)(CH_2CH_2OSO_2CH_3)$ ·Pc. s.[e]	7.5	5	0.5	15	5×10^{-5}
840	$CH_3-N(CH_2CH(CH_3)OSO_2CH_3)(CH_2CH(CH_3)OSO_2CH_3)$ ·Pc. s.[e]	37.5	25	1	37.5	5×10^{-3}
838	$CH_3-N(CH_2CH_2CH_2OSO_2CH_3)(CH_2CH_2CH_2OSO_2CH_3)$ ·HCl	75	50	1	75	2.5×10^{-2}
844	$(CH_3)(CH_3)N(CH_2CH_2CH_2OSO_2CH_3)(CH_2CH_2CH_2OSO_2CH_3)$ ·Pc. s.[e]	37.5	25	—	—	1×10^{-1}

a) Maximum tolerance dose on rats bearing *Yoshida sarcoma*.
b) Minimum effective dose determined by the method reported by Yoshida, *et al.*: Gann, **45**, 489 (1954).
c) Chemotherapeutic index.
d) Minimum effective concentration in tissue culture, determined by the method reported by M. Ishidate, *et al.*: This Bulletin, **7**, 873 (1958).
e) Picryl sulfonate.

1) J.M. Sprague: Chem. Abst., **49**, 1776 (1955).

picrylsulfonate, m.p. 161~162° (from H_2O. *Anal.* Calcd. for $C_{13}H_{20}O_{15}N_4S_3$: C, 27.46; H, 3.52; N, 9.86. Found : C, 27.88; H, 3.55; N, 9.89), and 2,2′-dihydroxy-N-methyldipropylamine yielded 2,2′-dimesyloxy-N-methyldipropylamine (No. 840) isolated as its picrylsulfonate, m.p. 150° (from Me_2CO-EtOH. *Anal.* Calcd. for $C_{15}H_{24}O_{15}N_4S_3$: C, 30.20; H, 4.03; N, 9.34. Found : C, 30.02; H, 4.02; N, 9.35), and 3,3′-dihydroxy-N-methyldipropylamine yielded 3,3′-dimesyloxy-N-methyldipropylamine (No. 838) isolated as its hydrochloride, m.p. 95° (from MeOH-Et_2O. *Anal.* Calcd. for $C_9H_{22}O_6NS_2Cl$: C, 31.76; H, 6.47; N, 4.12. Found : C, 31.80; H, 6.73; N, 3.99). By the reaction with methyl iodide in ether, the free base No. 838 yielded 3,3′-dimesyloxy-N-dimethyldipropylammonium salt (No. 844) isolated as picrylsulfonate, m.p. 65~75° (from Me_2CO-EtOH. *Anal.* Calcd. for $C_{16}H_{26}O_{15}N_4S_3$: C, 31.42; H, 4.42; N, 9.17. Found : C, 31.31; H, 3.93; N, 8.88).

The compounds and their biological data so far obtained are summarized in Table I. Out of these compounds, No. 838 was of particular interest as its antitumor activity on *Yoshida sarcoma* was found to be of the same order as that of methyl-bis 2-chloroethyl amine N-oxide. Further investigation is in progress and details of this work will be published in the near future.

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Partial Synthesis of Securinine

The structure (I) of securinine, a major alkaloid of *Securinega suffruticosa* REHD., has been established by the recent works (the constitution,[1] relative[2] and absolute configuration[3]). This alkaloid possesses a clinically useful strychnine-like activity, which makes us interested in its synthesis. The present report concerns with the partial synthesis of securinine from the degradation products (II) and (III),[2] involving reconstitution of the 6-azabicyclo[3.2.1]octane system.

Bromination of the hydrochloride monohydrate of II,[2] m.p. 218~220°, $[\alpha]_D^{25}$ +94.8° (c=1, EtOH), with bromine in chloroform gave a 71% yield of the hydrochloride of the

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