3,3′-Dimesyloxy-N-methyl[^{14}C]dipropylamine Hydrochloride (III)——A solution of II (400mg.) in CH_3CN (15 ml.) was added with stirring into a solution of methanesulfonic acid anhydride (2 g.) in CH_3CN (15 ml.) at room temperature. After stirring the mixture for 24 hr. the solvent was evaporated *in vacuo*, the residue was dissolved in a mixture of abs. EtOH containing HCl in 5*N* concentration (10 ml.) and ether (25 ml.), and kept overnight at −5°. The separated crystals (560 mg.) were recrystallized twice from MeOH-Et_2O to give pure crystals, of III (273 mg.) in 29% yield. m.p. 94~95°. *Anal.* Calcd. for a cold sample synthesized by the same method for $C_9H_{22}O_6NS_2Cl$: C, 31.76; H, 6.47; N, 4.12. Found : C, 31.48; H, 6.34; N, 4.10.

Radioactive purity was defined by the technique of paper chromatography and autoradiography which revealed a single spot. The specific activity was 1.84×10^6 c.p.m./mg. measured by the liquid scintillation method using a Packard Tri-Carb liquid scintillation spectrometer.

Recovery of unreacted II : The mother liquid from the crystallization of III was evaporated and the residue was hydrolyzed with 10% aq. NH_4OH. After removal of the solvent, the residue was absorbed on Amberlite IR-120 (H^+ form) and eluted with 5% NH_4OH-MeOH. Evaporation of the solvent gave an oil (272 mg.) identical with II when examined by paper chromatography.

The author expresses his thanks to Dr. Y. Sakurai, Prof. Z. Tamura, and Dr. T. Nambara for their kind advices and cooperation.

Summary

A simple method was described for the synthesis of 3,3′-dimesyloxy-N-methyl[^{14}C]-dipropylamine hydrochloride in 29% yield, together with a method for recovery of the aminoalcohol (II) from the impure dimesyloxy derivative.

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Yoshio Sakurai*1 and Mahmoud M. El-Merzabani*2 : Carcinostatic Activity of Several New Derivatives of Sulfonic Acid Esters of Some Aminoglycols.

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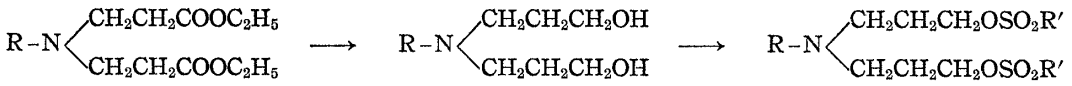
As an appendix to our preceding paper,[1] this brief note deals with the preparation of several sulfonic acid esters of aminoglycols, together with their inhibitory effect on Yoshida sarcoma.

The compounds and their screening data against Yoshida sarcoma are shown in Table I. All the tested compounds showed strong cytomorphological effect, specially compound No. 858, but none of them had any noticeable prolongation effect on the life span of rats bearing the same tumor. Compound No. 860 almost lost its activity when administered orally.

The method used in the preparation of these compounds was as follows;



R=C_2H_5–, C_6H_{11}–, $C_6H_5CH_2$–, R′=CH_3–, C_6H_5–, $CH_3C_6H_5$–

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1) Y. Sakurai, M. M. El-Merzabani : This Bulletin, **12**, 954 (1964).

Table I. Screening Data of Sulfonic Acid Esters against Yoshida Sarcoma

Compound No.	Formula	*in vivo* LD$_{50}$	MTD[b]	MED[c]	CI[d]
859[a]	$C_2H_5N(CH_2CH_2CH_2OSO_2CH_3)_2 \cdot HCl$	375	250	10	37.5
861[a]	$C_6H_5NH(CH_2CH_2CH_2OSO_2CH_3)_2 \cdot HCl$	375	250	10	37.5
858[a]	$C_6H_5CH_2N(CH_2CH_2CH_2OSO_2CH_3)_2 \cdot HCl$	375	250	0.5	750
862[a]	$C_6H_5N(CH_2CH_2CH_2OSO_2CH_3)_2 \cdot HCl$	37.5	25	0.5	75
863	$C_6H_5N(CH_2CH_2CH_2OSO_2C_6H_5)_2$	>750	>500	25	> 30
860	$C_6H_5N(CH_2CH_2CH_2OSO_2C_6H_4CH_3)_2 \cdot HCl$	>750	>500	10	> 75

a) Sirup
b) Maximum tolerance dose on rats bearing Yoshida Sarcoma.
c) Minimum effective dose determined by the method by Yoshida, *et al.*: Gann, **45**, 489 (1954).
d) Chemotherapeutic index.

Bis(2-carboethoxyethyl)alkylamine were prepared by the condensation of the corresponding alkylamine with ethylacrylate in abs. EtOH. Except for ethylamine, the products were usually mixtures of mono- and disubstituted ones, but purification was easily attained by fractional distillation. The phenyl derivative was prepared by the reaction of 2-bromoethyl propionate with aniline after description by Thayer & Mc-Elvain.[2]

Experimental

3,3'-Dihydroxy-N-ethyldipropylamine (I)——By reduction of bis (2-carboethoxyethyl) ethylamine (0.05*M*, b.p$_{11\sim12}$ 145~146°) with $LiAlH_4$ (0.12*M*) in abs. ether (500 ml.). b.p$_6$ 141~142°. *Anal.* Calcd. for $C_8H_{19}O_2N$: C, 59.59; H, 11.88; N, 8.69. Found: C, 59.07; H, 11.90; N, 8.52.

3,3'-Dihydroxy-N-cyclohexyldipropylamine (II)——By reduction of bis(2-carboethoxyethyl)cyclohexylamine (0.05*M*, b.p$_{11\sim12}$ 194~195°) with $LiAlH_4$ (0.12*M*) in ether (500 ml.) .b.p$_2$ 194~196°. *Anal.* Calcd. for $C_{12}H_{25}O_2N$; N, 6.51. Found: N, 6.82.

3,3'-Dihydroxy-N-benzyldipropylamine (III)——By reduction of bis (2-carboethoxyethyl) benzylamine (0.1*M*, b.p$_2$ 180~182°) with $LiAlH_4$ (0.22*M*) in ether (800 ml.). b.p$_{0.43}$ 160~160.5°. *Anal.* Calcd. for $C_{13}H_{21}O_2N$: C, 69.92; H, 9.48; N, 6.27. Found: C, 69.54; H, 9.40; N, 6.26.

3,3'-Dihydroxy-N-phenyldipropylamine (IV)——By reduction of bis (2-carboethoxyethyl) phenylamine (0.05*M*, b.p$_4$ 175~176°) with $LiAlH_4$ (0.12*M*) in ether (500 ml.). m.p. 61.5~62° (from ether/Petr. ether).

3,3'-Dimesyloxy-N-ethyldipropylamine (No. 859)——By the reaction of methanesulfonic anhydride (8 g.) with I (3.4 g.) in CH_3CN (50 ml.). Isolated as picryl sulfonate. m.p. 127~128° (from acetone/EtOH). *Anal.* Calcd. for $C_{16}H_{26}O_{15}N_4S_3$: C, 31.48; H, 4.29; N, 9.17. Found: C, 31.65; H, 4.15; N, 8.82.

3,3'-Dimesyloxy-N-cyclohexyldipropylamine (No. 861)——From II (4.3 g.) and methanesulfonic anhydride (7.2 g.) in CH_3CN (25 ml.). Isolated as sirup hydrochloride partially purified. *Anal.* Calcd. for $C_{14}H_{30}O_6NS_2Cl$: C, 41.23; H, 7.41; N, 3.43. Found: C, 42.11; H, 7.20; N, 3.90.

3,3'-Dimesyloxy-N-benzyldipropylamine (No. 858)——From III (4 g.) and methanesulfonic anhydride (5 g.) in CH_3CN (50 ml.). Isolated as sirup hydrochloride. *Anal.* Calcd. for $C_{15}H_{26}O_6S_2Cl$: C, 43.33; H, 6.30; N, 3.37. Found: C, 43.55, 43.16; H, 6.44, 6.81; N, 4.29.

3,3'-Dimesyloxy-N-phenyldipropylamine (No. 862)——To an ice cold solution of IV (5 g.) in dry pyridine (50 ml.), methanesulfonyl chloride (6 g.) was added gradually with stirring. Stirring continued for 3 hr. $CHCl_3$ (100 ml.) was then added with 10% H_2SO_4 (200 ml.). The organic layer was separated, washed successively with H_2O, 10% $NaHCO_3$, and then H_2O. After drying on anhyd. Na_2SO_4, the solution was

2) J. R. Thayer, S. M. Mc-Elvain: J. Am. Chem. Soc., **49**, 2862 (1927).

evaporated to dryness. The colorless sirup remained was converted to picrylsulfonate. m.p. 161~162° from actone/EtOH. *Anal.* Calcd. for $C_{20}H_{26}O_{15}N_4S_3$: C, 36.48; H, 3.98; N, 8.51. Found; C, 36.73; H, 4.13; N, 8.23.

3,3'-Dibenzenesulfonyloxy-N-phenyldipropylamine (No. 863)——Similarly for Ⅳ (4.1 g.) and benzenesulfonylchloride (7 g.) in pyridine (50 ml). Isolated as free base. m.p. 55.5~56.5° (ether/Petr. ether). *Anal.* Calcd. for $C_{24}H_{27}O_6NS_2$: C, 58.89; H, 5.56; N, 2.86. Found : C, 58.89; H, 5.55; N, 2.91.

3,3'-Di-*p*-toxyloxy-N-phenyldipropylamine (No. 860)——Similarly from Ⅳ (5 g.) *p*-toluenesulfonyl chloride (10 g.) in pyridine (50 ml.). Isolated as hydrochloride. m.p. 107~108° (from acetone/Petr. ether). *Anal.* Calcd. for $C_{26}H_{32}O_6NS_2Cl$: C, 56.37; H, 5.82; N, 2.53. Found : C, 56.81; H, 6.01; N, 2.70.

The authors express their thanks to Drs. Z. Tamura and T. Nambara for their cooperation. Thanks also due to Mr. D. Ohata for microanalysis. This work was supported by a Grant-in-Aid of Scientific Research for 1964 from the Ministry of Health and Welfare which is greatly acknowledged.

Summary

Six new derivatives of sulfonic acid esters of aminoglycols were prepared and tested for their carcinostatic activity against Yoshida sarcoma. All the tested compounds showed strong cytomorphological effects on the tumor cells but not effective in prologation of life span of the tumor bearing animals.

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Yoshio Arata and Tsutomu Ohashi : Constituents of *Rhizoma Nupharis*. XXIII.*1 The Absolute Configuration of Nuphamine.*2

(*Faculty of Pharmaceutical Sciences, Kanazawa University**3)

A new alkaloid, nuphamine,[1,2] $C_{15}H_{23}O_2N$ isolated from the roots of *Nuphar japonicum* DC. has been given the formula (I), in which the remaining unsettled problem was the configuration about the side chain double bond. The present paper deals with the absolute configuration of nuphamine.

The action of thionyl chloride on nuphamine (I) gave a chloro compound (Ⅱ),[2] which, when kept standing in dilute hydrochloric acid, re-formed I. Attempts to direct toward the ring closure of Ⅱ to Ⅲ were unsuccessful recovering only the starting material, but when heated with potassium hydroxide in methanol solution, Ⅱ afforded O-methylnuphamine (Ⅳ) $C_{16}H_{25}O_2N$ (picrolonate : m.p. 178°). These facts suggested that I would be represented by the formula (Ⅶ).

Furthermore, the configuration was studied by the measurement of nuclear magnetic resonance spectra of I, Ⅳ and (−)-anhydronupharamine*4,3 (Ⅵ) derived from (−)-nupharamine (Ⅷ).

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*1 Y. Arata, *et al.* : This Bulletin, **13**, 1247 (1965).

*2 Presented in part the meeting of the Hokuriku Branch of the Pharmaceutical Society of Japan, Kanazawa, June 5th (1965).

*3 Takara-machi 13, Kanazawa (荒田義雄, 大橋 力).

*4 Reduction of Ⅵ gave desoxynupharamine (Ⅴ) derived from Ⅱ.

1) Y. Arata, T. Ohashi : This Bulletin, **13**, 392 (1965).

2) *Idem* : *Ibid.*, **13**, 1247 (1965).

3) *Idem* : Yakugaku Zasshi, **77**, 792 (1957); **79**, 127, 729, 734 (1959).