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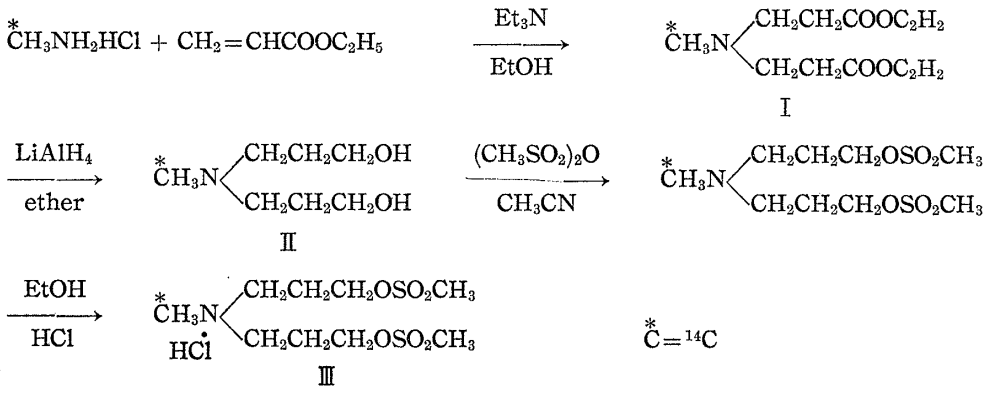
Mahmoud M. El-Merzabani: Synthesis of 3,3'-Dimesyloxy-N-methyl[^{14}C]dipropylamine Hydrochloride.

(*Faculty of Pharmaceutical Sciences, University of Tokyo*[*1])

The previous paper[1] reported the strong carcinostatic activity of 3,3'-dimesyloxy-N-methyldipropylamine hydrochloride (No. 838), which is now under clinical investigation. For experiments on its metabolic fate *in vivo*, the ^{14}C-labeled compound was prepared, starting from methylamine[^{14}C] by the following route.



The method used was essentially the same as that already reported[1] with some modification to suite the semimicro-scale process. To avoid the loss of methylamine-[^{14}C] during the reaction, trimethylamine was used to liberate the free methylamine-[^{14}C] in the reaction mixture. This procedure leads to the preparation of I in an almost quantitative yield (based on the methylamine[^{14}C] hydrochloride). By the reduction of I with a slight excess of lithium aluminum hydride, II was obtained in 95% yield. The mesylation was carried out by exactly the same process as previously reported.

On ascending paper chromatogram I, II, and III were located respectively at Rf 0.67, 0.32, and 0.4 (BuOH-AcOH-H_2O=4:1:1). The Rf values determined by autoradiography were quite similar to those detected by the Dragendorff reagent.

Experimental

Bis(2-carboethoxyethyl)-methyl[^{14}C]amine(I)——A mixture of $CH_3NH_2 \cdot HCl$[^{14}C] (3 mc., The Radioactive Centre, Amersham, England) (28 mg.), $CH_3NH_2 \cdot HCl$(27 2mg.), ethyl acrylate (2 ml.), and Et_3N (2 ml.) was kept at room temperature for 10 days. Ether (50 ml.) was added, the precipitated $Et_3N \cdot HCl$ was separated by filtration, and washed with ether (50 ml. × 3). The filtrate and the combined washings were evaporated first at ordinary atmospheric pressure, then at 3 mm. Hg below 70° to remove all the unreacted ethyl acrylate. The oily residue was used as such without purification for the next process.

3,3'-Dihydroxy-N-methyl[^{14}C]dipropylamine (II)——Ether solution of I was added dropwise with stirring into ether solution of $LiAlH_4$ (600 mg.). After 24 hr., H_2O (2 ml.) was added cautiously with stirring to decompose excess $LiAlH_4$. The precipitated $Al(OH)_3$ was separated by filtration and washed 3 times with ether (50 ml.). The oil remaining after evaporation of ether from the extract and washing was absorbed on a short column of Amberlite IR-120 (H^+ form), and eluted with 5% NH_4OH-MeOH.

By evaporation of the solvent II was obtained as an oily product, which gave one spot on paper chromatogram. Yield, 615 mg. (95%).

*1 Hongo, Bunkyo-ku, Tokyo.

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

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.

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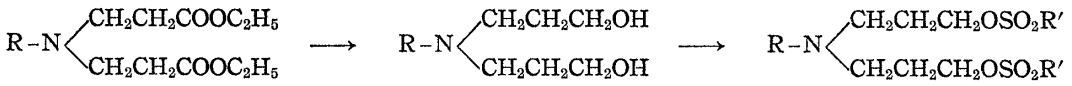
Yoshio Sakurai*1 and Mahmoud M. El-Merzabani*2 : Carcinostatic Activity of Several New Derivatives of Sulfonic Acid Esters of Some Aminoglycols.

(*Cancer Institute, The Japanese Foundation for Cancer Research**1 *and Faculty of Pharmaceutical Sciences, University of Tokyo**2)

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–, $CH_3C_6H_5$–

*1 2615, Nishisugamo 2-chome, Toshima-ku, Tokyo (桜井欽夫).

*2 Hongo, Bunkyo-ku, Tokyo. This paper was submitted to the annual meeting of Japanese Cancer Society, November, 1964, Tokyo.

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