N-(4-Biphenyl)-N-(2-diethylaminoethyl)-mandelamide Hydrochloride. A Potent Local Anesthetic for Use with Sulfhydryl Inhibitors for Cancer Therapy[1]

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Selected sulfhydryl inhibitors have regressed a variety of human cancers without injury to hematologic status and wound healing or with actual improvement in hematologic status in some patients.[2,3] Rapid acting sulfhydryl inhibitors of the arsenoso and iodoacetyl type can cause much pain on intravenous infusion or intratumor injection, so that potent local anesthetics for concomitant use are at times needed. For this purpose, N-(4-biphenylyl)-N-(2-diethylaminoethyl)mandelamide hydrochloride (I) has been clinically useful. In sensitivity tests against a variety of animal and human cancer cells, it can significantly potentiate the activity of clinically useful sulfhydryl inhibitors.[4]

Biological Activity.—By intradermal wheal tests in animals and humans, activity of I is about ten times as great as that of procaine, about five times as great as that of lidocaine. A 0.2% solution of I is approximately equivalent in activity to 1.0% lidocaine. Toxicity of I closely approximates that of lidocaine on intravenous injection in mice and exceeds somewhat that of procaine.

In the guinea pig sciatic nerve block test, 0.25 ml of a 1.0% solution of I placed directly on the isolated nerve produced mean duration of activity of 27 ± 11.2 hr, by contrast with minutes for other commonly used anesthetics. Anticholinergic activity of I is very weak. The *in vitro* atropine ratio is 0.00008. There is no apparent effect on acetylcholine in cardiovascular–respiratory tests. The curaremimetic activity of I is very low, the curare ratio in the frog rectus test being 0.15. The compound is inactive in the electroshock and pentylenetetrazole anticonvulsant tests.

Clinical trial with 30 patients has shown that I is not suitable for use in standard nerve block anesthesia because of low diffusibility and tendency to cause irritation in high concentrations.

For direct intratumor injection with sulfhydryl inhibitors, however, for which sulfhydryl inhibitor and I are dissolved together in the same solution and injected simultaneously, low diffusibility has presented no clinical problems while high potency and relatively low toxicity of I offer significant advantages over other available local anesthetics.

Experimental Section[5]

N-(4-Biphenylyl)-N-(2-diethylaminoethyl)mandelamide.—A 10% excess of acetylmandelyl chloride[6] in a twofold volume of dry benzene was slowly added to a solution of N-(4-biphenylyl) N′,N′-diethylethylenediamine[7] in a twofold volume of dry benzene, with good stirring and cooling to keep the temperature below 20°. Reaction was completed by refluxing for 1 hr. After cooling, a fourfold volume of ligroin (bp 66–75°) was added to complete separation of the crude product. Yield of crude product, mp 175–179°, was 97%. The product was purified by solution in 50% alcohol–acetone and precipitation with ether, to give a product of mp 185–186°. The acetyl group was removed by refluxing for 1 hr with a 10% excess of NaOH in 50% aqueous ethanol. The product was evaporated to dryness, taken up in ether, and washed several times with water, and the ether was evaporated to give the viscous, pale yellow base. This was dissolved in five times its weight of absolute methanol, and the stoichiometric quantity of 9.0 *N* solution of dry HCl in absolute methanol was added. The clear colorless solution was diluted to incipient cloudiness with absolute ether and allowed to stand at 5° for 24 hr. The precipitate was redissolved in absolute methanol and the precipitation with absolute ether was repeated. After drying the precipitate for 24 hr at 70°, the yield of product melting at 169–170° was 90%. The last trace of solvent was removed by drying over P_2O_5 *in vacuo* at 78° for 24 hr to give a hygroscopic product melting at 176–177°.

Anal. Calcd for $C_{26}H_{31}N_2O_2Cl$: C, 71.15; H, 7.07; N, 6.39. Found: C, 71.16; H, 7.24; N, 6.22.

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(5) Melting points were taken in capillary tubes by means of a stirred oil bath and are corrected. Bioassays were performed by Merck Sharp and Dohme, Rahway, N. J. Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

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Sulfate Esters of 5-Iododeoxyuridine and 5-Iododeoxycytidine[1]

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In view of the reported biological activities of the sulfate esters of several nucleosides,[2-6] and because of interest in halogenated pyrimidine deoxyribonucleosides[7-9] and deoxyribonucleotides[8,10] in this laborae

TABLE I
SULFATION OF IUdR AND ICdR

Product	Yield, mole %: $HOSO_2Cl$, r[a] 1.6	$HOSO_2Cl$, r 2.5	PST, r 1.6	PST, r 2.5	R_f[b]
IUdR 3′-sulfate (A)	16	15	12	7	0.38
IUdR 5′-sulfate (B)	40	33	27	25	0.31
IUdR disulfate (C)	12	40	5	59	0.18
ICdR 3′-sulfate (A′)	4	11	9	8	0.45
ICdR 5′-sulfate (B′)	78	49	23	32	0.37
ICdR disulfate (C′)	12	28	5	57	0.23

[a] r = sulfating agent/nucleoside. [b] Solvent system: isobutyric acid–H_2O–concentrated NH_4OH (66:33:1).

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