[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF RICHMOND]

Local Anesthetics. IV. Aryl Urethans of 2-Methyl-2-monoalkylamino-1-propanols[1]

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In the study in this Laboratory of derivatives of aminoalkanols[3,4,5] it was observed that esters of 2-methyl-2-monoalkylamino-1-propanols were obtained as crystalline hydrochlorides more readily than esters of the other monoalkylaminoalkanols. Since also certain phenylurethans of dialkylaminoalkanols[6] and of 2-monoalkylaminoethanols[7] have been found to be effective as local anesthetics it seemed desirable to prepare the arylurethans of 2-methyl-2-monoalkylaminopropanols shown in Table I.

TABLE I

ARYL URETHANS OF 2-METHYL-2-MONOALKYLAMINO-1-PROPANOLS

$RNHCOOCH_2C(CH_3)_2NHR'$[a]

					Hydrochlorides		
		M. p. °C.	Nitrogen, %		M. p. °C.	Chlorine, %	
R	R'	(uncor.)	Calcd.	Found	(uncor.)	Calcd.	Found[b]
Phenyl	Ethyl	99–100	11.84	11.92	164–165	13.00	12.72
Phenyl	*n*-Propyl	78.5–80	11.19	11.40	206–207	12.36	12.31
Phenyl	*n*-Butyl	59.5–61	10.60	10.55	189–190	11.79	11.79
Phenyl	*n*-Amyl	43.5–46	10.06	9.80	183–184	11.26	11.39
Phenyl	*n*-Hexyl	Oil	...	...	162–163.5	10.78	10.73
Phenyl	*n*-Heptyl	Oil	...	...	156–157	10.34	10.39
Phenyl	*n*-Decyl	Oil	...	...	171–173	9.22	9.30, 9.30
Phenyl	iso-Amyl	77–78	10.06	10.28	191.5–192	11.26	11.15
o-Tolyl	*n*-Propyl	55–57	10.60	10.43	195–197	11.80	11.77, 11.70
o-Tolyl	*n*-Butyl	Oil	...	...	207–210	11.26	11.28, 11.35
o-Tolyl	*n*-Amyl	Oil	...	...	210–212	10.78	10.73, 10.80
o-Tolyl	*n*-Hexyl	54–55	9.14	9.35	172–174	10.34	10.39, 10.40
o-Tolyl	*n*-Heptyl	69–71	8.74	8.84	147–149	9.94	9.81, 9.81
p-Tolyl	*n*-Propyl	77–78	10.60	10.87	231–232	11.80	11.80, 11.80
p-Tolyl	*n*-Butyl	82–83	10.06	10.25	211–213	11.26	11.35, 11.31
p-Tolyl	*n*-Amyl	85–87	9.58	9.70	192–194	10.78	10.78, 10.80
p-Tolyl	*n*-Hexyl	56–57	9.14	9.12	189.5–190.5	10.34	10.41, 10.40
p-Tolyl	*n*-Heptyl	Oil	...	...	183–185	9.94	10.01, 10.01
α-Naphthyl	Ethyl	99–101.5	9.78	10.09	222–223.5	10.98	10.92, 10.94
α-Naphthyl	*n*-Propyl	68–70.5	9.33	9.63	232–233	10.53	10.39, 10.41
α-Naphthyl	*n*-Butyl	92.5–93.5	8.91	8.94	223.5–225	10.11	9.94
α-Naphthyl	*n*-Amyl	63.5–64.5	8.53	8.61	212–213.5	9.72	9.73
α-Naphthyl	*n*-Hexyl	78–79.5	8.18	7.95	213–214.5	9.36	9.39
α-Naphthyl	*n*-Heptyl	60–62	7.86	7.73	196.5–198	9.02	9.12
β-Naphthyl	*n*-Propyl	103–104	9.33	9.44	175–177	10.53	10.26, 10.26
β-Naphthyl	*n*-Butyl	91–92	8.91	9.05	177–179	10.11	10.17, 10.19
β-Naphthyl	*n*-Amyl	105–107	8.53	8.45	194–196	9.72	9.79, 9.79
β-Naphthyl	*n*-Hexyl	89–91	8.18	7.93	193–195	9.36	9.36, 9.33
β-Naphthyl	*n*-Heptyl	74–76	7.86	7.84	189–191	9.02	9.11, 9.09

[a] Grateful acknowledgment is made to Hugh Adair, S. M. King, Randell Q. Little and Edwin Worsham for assistance in the preparation of several of these compounds. [b] The chloride analyses were performed by Irene White and Robert L. Kersey.

The urethan hydrochlorides listed above were prepared by the reaction of phenyl-, *p*-tolyl-, *o*-tolyl, α-naphthyl- and β-naphthyl isocyanates with 2-methyl-2-monoalkylamino-1-propanol hydrochlorides, usually in chloroform solution.

Procedure A

2-Methyl-2-mono-*n*-hexylaminopropyl-*p*-tolylurethan Hydrochloride (A), $p\text{-}CH_3C_6H_4NHCOOCH_2C(CH_3)_2NHC_6H_{13}\cdot HCl$.—A solution of 34.7 g. (0.2 mole) of 2-methyl-2-mono-*n*-hexylamino-1-propanol in 75 ml. of chloroform was saturated with dry hydrogen chloride.[8] To this solution was added 26.6 g. (0.2 mole) of *p*-tolyl isocyanate

(1) Acknowledgment is made to Dr. E. Emmet Reid, Research Adviser to the Chemistry Department of the University of Richmond, for his advice in this work.

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(3) Pierce, Salsbury and Fredericksen, THIS JOURNAL, **64**, 1691–1694 (1942).

(4) Pierce, Salsbury, Haden and Willis, *ibid.*, **64**, 2884–2885 (1942).

(5) Pierce, Haden and Gano, *ibid.*, **67**, 408–409 (1945).

(6) Rider, *ibid.*, **52**, 2115–2118 (1930); Rider, U. S. Patent 2,033,740 (1936); Christiansen and Harris, U. S. Patent 2,137,042 (1938); Lott and Braker, U. S. Patent 2,109,492 (1938).

(7) Cope and Hancock, THIS JOURNAL, **66**, 1450 (1944).

(8) The amino alcohol hydrochloride also was formed by addition of excess hydrochloric acid to the amino alcohol, removal of the water and excess acid by vacuum evaporation, addition of toluene and continued evaporation. This method was more rapid but less satisfactory than the one given above.

and the mixture was refluxed for seventeen hours.[9] The reaction mixture was added slowly to one liter of hot water and the chloroform was evaporated off. Sodium hydroxide was added and the oil which separated, on standing became semi-solid. The product was separated from the aqueous solution and stirred with 300 ml. of ether. The ether solution was filtered into one liter of *N* hydrochloric acid. Almost immediately a precipitate of 2-methyl-2-mono-*n*-hexylaminopropyl-*p*-tolylurethan hydrochloride (A) came out of solution.[10] The ether was allowed to evaporate and the precipitate was filtered with suction, washed with ether and air dried; yield, 35.1 g., 51%. Without further purification the product had a melting point of 188–189° and gave a fair chloride analysis. *Anal.* Calcd. for $C_{18}H_{30}N_2O_2 \cdot HCl$: chloride, 10.34. Found: chloride, 10.04, 10.04.

In another similar run the chloride analysis of the precipitate from hydrochloric acid was 10.24 and 10.25%.

The product was recrystallized to constant melting point from 95% ethanol.

By a similar procedure, 2-methyl-2-mono-*n*-amylaminopropyl-*p*-tolylurethan hydrochloride was prepared and precipitated in hydrochloric acid solution in a yield of 36.2 g., 55%. This first precipitate gave a chloride analysis 0.5% below theory and a melting point of 186–190°.

Procedure B

2-Methyl-2-monoethylaminopropylphenylurethan Hydrochloride (B), $C_6H_5NHCOOCH_2C(CH_3)_2NHC_2H_5 \cdot HCl$. —An ether solution of 11.7 g. (0.1 mole) of 2-methyl-2-monoethylamino-1-propanol was treated with dry ethereal hydrogen chloride to precipitate the amino alcohol hydrochloride. The salt was filtered off and heated under reflux for three hours with 11.9 g. (0.1 mole) of phenyl isocyanate, dissolved in 200 ml. of tetrachloroethane. Upon removal of the solvent under reduced pressure the resulting viscous green oil displayed no tendency to crystallize, even after standing for two weeks in the refrigerator and being seeded. The oil was shaken with 10% sodium carbonate solution and alcohol free ether and the ether solution of the free base was dried over sodium sulfate. The urethan hydrochloride was precipitated from the ether solution by addition of ethereal hydrogen chloride. A green gummy oil which separated was vacuum dried for two hours at 70° and 10 mm. On cooling, the product solidified. It was recrystallized to constant melting point from a solution of *n*-heptane and dry reagent grade acetone; yield, 7.0 g., 25.6%. The crystals thus obtained are colorless rods.

The other low molecular weight urethan hydrochlorides usually were recrystallized from a solution of acetone, water and ether. Ethanol or ethanol and acetone served satisfactorily as solvents for the recrystallization of most of the urethan hydrochlorides of higher molecular weight.

The urethans were prepared from the pure urethan hydrochlorides by dissolving the salt in warm ethanol and adding this solution to an aqueous solution of sodium hydroxide or by dissolving the salt in hot water and adding sodium hydroxide solution. The urethan thus liberated was separated from the aqueous solution by filtration or ether extraction.

The anesthetic action of the hydrochlorides of the phenylurethans and α-naphthylurethans has been tested by Drs. Ramsey and Haag,[11] of the Medical College of Virginia. Tests on the anesthetic action of the *o*-tolyl-, *p*-tolyl- and β-naphthylurethans will be carried out by Dr. Haag and associates and will be reported elsewhere.

Summary

A series of phenyl-, *o*-tolyl-, *p*-tolyl-, α-naphthyl- and β-naphthylurethans of 2-methyl-2-monoalkylamino-1-propanols and their hydrochlorides are described.

RICHMOND, VIRGINIA RECEIVED JANUARY 3, 1949

(9) A few of the urethans were prepared by heating a chloroform solution of an aryl isocyanate and amino alcohol hydrochloride in a sealed tube at approximately 100° overnight. Since considerable pressure was built up by this process, it was not as satisfactory as the gentle refluxing of a chloroform solution of the reactants.

(10) The higher molecular weight urethan hydrochlorides are so insoluble in hydrochloric acid solution that there is little loss in isolating them by this method. Urethans of intermediate molecular weight are partially precipitated by this method. Data are given on a few runs to illustrate this fact. 2-Methyl-2-monopropylaminopropyl-*p*-tolylurethan hydrochloride was obtained in 20% yield in the precipitate from the hydrochloric acid solution and, in addition, in 31% yield by working up the aqueous solution by the method described just below for low molecular weight urethans. 2-Methyl-2-mono-*n*-butylaminopropyl-*p*-tolylurethan yielded 35% of the theoretical amount in the precipitate from hydrochloric acid and only a trace of oily product from the aqueous solution. 2-Methyl-2-mono-*n*-butylaminopropyl-α-naphthylurethan gave a yield of 36% in the precipitate from hydrochloric acid leaving 1.4% dissolved in the acid solution.

Urethans which did not precipitate satisfactorily as the hydrochloride from aqueous solutions usually were isolated by solution of the hydrochloride in water, precipitation of the free base with alkali, solution of the free base in isopropyl ether and precipitation of the hydrochloride with dry hydrogen chloride. This method served satisfactorily for all of the lower molecular weight urethan hydrochlorides on which it was tried except 2-methyl-2-ethylaminopropylphenylurethan hydrochloride (B), which came out of isopropyl ether as an oil when the solution of the free base was treated with dry hydrogen chloride. This particular urethan hydrochloride was obtained in a crystalline form by Procedure B..

(11) Ramsey and Haag, *J. Pharmacol. Exp. Therap.*, **91**, 190–193 (1947).