[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

THE SYNTHESIS OF CERTAIN 4-DIALKYLAMINO-1-(1-NAPHTHYL)-1-BUTANOLS[1]

BYRON RIEGEL, R. I. JACKSON, J. G. SANDZA, AND L. T. SHERWOOD, JR.

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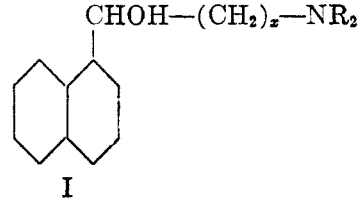
In the course of investigating various types of compounds as possible antimalarials, it was suggested by Dr. Lyndon F. Small that a series of ω-dialkylamino-1-(1-naphthyl)-1-alkanols (I) be prepared in which R is a straight-chain primary alkyl group containing one to eight carbons and X is 3, 4, or 5. Seven compounds in which X is 3 have been prepared in this Laboratory and submitted for testing.



I

The general method of preparation is that of Marxer (1) and Small (2) and consists of preparing the Grignard reagent from the proper 1-chloro-3-dialkylaminopropane and treating it with 1-naphthaldehyde. Distilling twice at about 10^{-3} mm. gives a pure product. The results of these preparations are summarized in Table I.

Attempts to prepare derivatives of the hydroxyl group in these carbinols were not successful because of their tendency to lose the elements of water. To establish whether this took place during the distillation, especially for the higher members, micro Zerewitinoff determinations were made for active hydrogen. These are given in Table II. Since none of these compounds proved to be effective antimalarials the series where X was 4 or 5 was not prepared.

EXPERIMENTAL

1-Chloro-3-dialkylaminopropanes. These compounds were prepared by essentially standard procedures from 1-bromo-3-chloropropane and the appropriate amine (2).[2]

4-Dialkylamino-1-(1-naphthyl)-1-butanols (General Procedure). Excess magnesium was placed in a one-liter 3-necked flask and rinsed with anhydrous ether. Fifty to 100 ml. of dry ether was distilled into the flask from an ether solution of ethylmagnesium bromide and, with stirring, a few crystals of iodine and 1 ml. of butyl bromide were added. When the reaction subsided, an additional 1 ml. of butyl bromide was added and, as soon as the reaction became vigorous, the 1-chloro-3-dialkylaminopropane (about ⅓ mole) was added over a period of one to two minutes. During the next half hour, 100 to 250 ml. of dry ether was distilled into the flask and the mixture was stirred and heated to gentle refluxing for 14 to

[1] The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Reearch and Development and Northwestern University.

[2] We are indebted to Dr. R. C. Elderfield for furnishing us with the dialkylamines.

18 hours. The Grignard reagent from the higher molecular weight amines seemed to be formed more rapidly and in better yields, probably because of their greater solubility in ether.

Sufficient ether was then distilled into the mixture to give a total volume of 400 to 700 ml. and the 1-naphthaldehyde was added, one-half to one ml. at a time, until further additions caused no refluxing. About half the ether was distilled back into the ethylmagnesium bromide solution and was replaced with ordinary ether. The mixture was decomposed with a saturated ammonium chloride solution.

TABLE I

DIALKYLAMINONAPHTHYLBUTANOLS

R	% YIELD (PURE)	DISTILLATION TEMP. AT 10^{-3} MM.	M.P. °C	N	
				CALC'D	FOUND[a]
CH_3—	51	160	62–63	5.76	5.57
C_2H_5—[b]	23			5.16	5.03
C_3H_7—	58	180–220	46–50[c]	4.68	4.61
C_5H_{11}—	21	187–195	oil	3.94	4.12
C_6H_{13}—	38	200	oil	3.65	3.81
C_7H_{15}—	46	215–225	oil	3.40	3.50
C_8H_{17}—	53		oil	3.19	3.64

[a] The microanalyses were performed by F. Marx and Lois E. May of Columbia University and by Margaret Ledyard of Northwestern University.

[b] This compound was previously prepared by Marxer (*loc. cit.*). It was distilled at 158–164° at 0.07 mm. and melted at 59–62°.

[c] This material could not be recrystallized. The melting point was taken on the solidified distillate.

TABLE II[a]

DETERMINATION OF ACTIVE HYDROGEN

R	G. USED	MOLES OF METHANE	
		Calc'd	Found
CH_3—	0.0392	1.64×10^{-4}	1.78×10^{-4}
C_6H_{13}—	0.0631	1.65×10^{-4}	1.525×10^{-4}
C_7H_{15}—	0.1292	3.14×10^{-4}	3.24×10^{-4}
C_8H_{17}—	0.0132	3.0×10^{-5}	2.8×10^{-5}

[a] We are indebted to Mr. A. H. Schlesinger for assistance in these determinations

To work up the dimethyl, diethyl, and dipropyl compounds, the ether solution was decanted from the magnesium and the magnesium salts and extracted with ice and 4 *N* hydrochloric acid until the extract was acid to Congo Red. Excess potassium hydroxide solution was added to the acid extract and the mixture was extracted three times with ether. The extracts were dried with anhydrous potassium carbonate and the ether removed. The residue was heated to 130–140° at 2–3 mm. and distilled twice at 10^{-3} mm.

The remaining compounds were worked up by the following procedure. The ether solution was washed with ice and 4 *N* hydrochloric acid until the washings were acid to Congo Red. To the remaining one or two layers (depending on the product and the amount of ether present) was added 150 to 200 ml. of petroleum ether (b.p. 60–70°) and the solutions

were mixed thoroughly. The upper (petroleum ether) layer was discarded and the lower was treated with excess potassium hydroxide solution. The product layer was separated and the aqueous layer was extracted twice with ether. The ether extract was added to the product, dried over potassium carbonate, and the ether was removed. The residue was distilled in the same manner as the lower molecular weight compounds.

All attempts to prepare crystalline salts of these compounds with hydrochloric acid, sulfuric acid, picric acid, and 4,4′-methylene-bis-(3-hydroxy-2-naphthoic acid) failed.

SUMMARY

A series of 4-dialkylamino-1-(1-naphthyl)-1-butanols were prepared by the reaction of 1-naphthaldehyde with 3-dialkylaminopropylmagnesium chloride. They proved ineffective as antimalarials.

EVANSTON, ILL.

REFERENCES

(1) MARXER, *Helv. Chim. Acta*, **24**, 209E (1941).
(2) L. F. SMALL, private communication.