[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF CALIFORNIA, LOS ANGELES]

SUBSTITUTED α-DIALKYLAMINOALKYL-1-NAPHTHALENEMETHANOLS. VII. SYNTHESIS OF SOME PROPANOLAMINES BY MEANS OF GRIGNARD REAGENTS[1]

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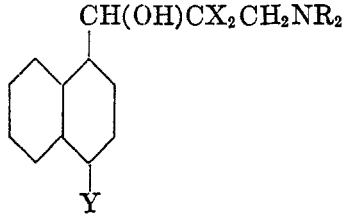
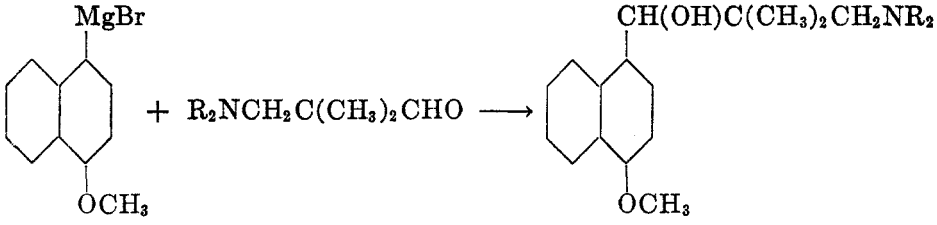
In the synthesis of β-dialkylaminoethyl-1-naphthalenemethanols, I,



I

the failure of the method involving preparation and reduction of the Mannich ketones (1) in those cases where Y = Cl, X = H or Y = CH_3O, X = CH_3 led to the investigation of other methods.

The synthesis of compounds representative of this second case (Y = CH_3O, X = CH_3) was accomplished successfully by treatment of α,α-dimethyl-β-dialkylaminopropionaldehyde with 4-methoxy-1-naphthylmagnesium bromide:



The α,α-dimethyl-β-dialkylaminopropionaldehydes were readily prepared according to the method of Mannich, Lesser, and Silten (2). The preparation of several of these compounds has been recorded in the literature: methylamino (3), dimethylamino (2), diethylamino (2), piperidino (2), and morpholino (4). We have extended the series to include those amino aldehydes containing the di-*n*-propyl, di-*n*-butyl, and di-*n*-amyl groupings. The properties of these compounds are summarized in Table I.

The Grignard reagent prepared from 1-bromo-4-methoxynaphthalene (5) re-

[1] This work was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of California, Los Angeles. The survey number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activity of those compounds to which such numbers have been assigned will be tabulated in a forthcoming monograph.

TABLE I

PROPERTIES OF α,α-DIMETHYL-β-DIALKYLAMINOPROPIONALDEHYDES

NR_2 R =	YIELD, %	B.P., °C	n^{20}	ANALYSIS			
				Calc'd		Found	
				% C	% H	% C	% H
C_3H_7	70	103–107/20 mm.	1.4363	71.30	12.51	71.23	12.38
C_4H_9	57	120–125/15 mm.	1.4415	73.18	12.76	73.10	12.72
C_5H_{11}	49	138–146/10 mm.	1.4440	74.62	12.94	74.71	13.12

TABLE II

PROPERTIES OF α-(2-DIALKYLAMINO-*tert.*-BUTYL)-4-METHOXY-1-NAPHTHALENEMETHANOLS

SN	R	YIELD, %	M.P. OF HYDROCHLORIDE, °C	ANALYSIS			
				Calc'd		Found	
				% C	% H	% C	% H
8768	C_2H_5	72[a]	(α) 107.5–109.0[b] (β) 170.0–170.4	68.26	8.59	68.11	8.71
8364	C_3H_7	51[a]	182.0–182.5	69.54	9.02	69.02	8.98
7993	C_4H_9	52[a]	166.0–167.0	70.64	9.39	70.68	9.13
8989	C_5H_{11}	45[c]		78.14	10.34	77.83	10.55

[a] This figure represents the yield of crude product.

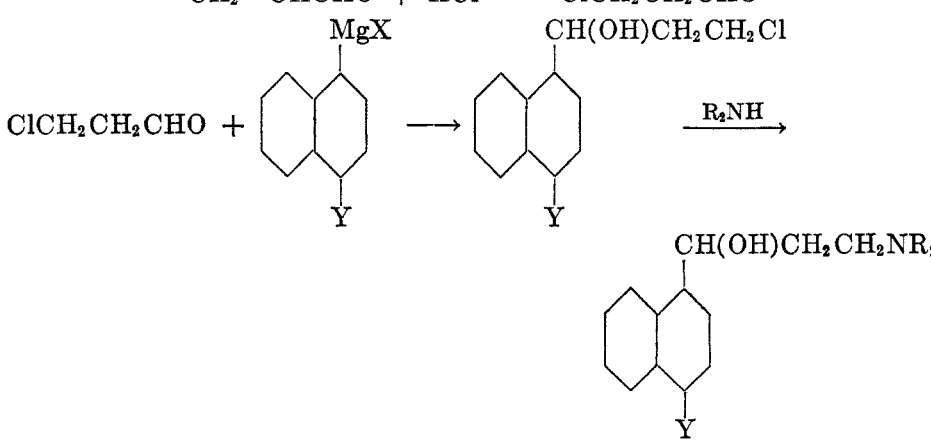
[b] Two dimorphic forms were obtained in this case. Mixed melting point was 169–171°.

[c] This figure represents the yield of distilled product. The hydrochloride could not be obtained solid.

acted smoothly with these aldehydes and four amino alcohols were prepared.[2] Table II lists the properties of these compounds.

The method of Fourneau (7, 8) was used to prepare the compounds where Y = CH_3O or Cl, X = H. This method is represented by the following equations:

$$CH_2{=}CHCHO + HCl \longrightarrow ClCH_2CH_2CHO$$



[2] Evidently the only other study of the reaction of a Grignard reagent with β-amino aldehydes is that of Matti and Barman (6) who treated α,α-dimethyl-β-dimethyl- and -diethyl-aminopropionaldehydes with ethyl, butyl, and phenyl Grignard reagents.

The synthesis of β-chloropropionaldehyde from acrolein and hydrogen chloride has been described several times (7, 8, 9). This compound is relatively unstable and readily polymerizes to a trimer (10) or decomposes into acrolein and hydrogen chloride. It has usually been prepared by saturation of acrolein with hydrogen chloride cold, followed by distillation of the monomer, sometimes at reduced pressure. The distillate was then used directly in the Grignard reaction. The rapid polymerization of the monomer to trimer was troublesome, since the latter did not react smoothly with Grignard reagents. This trimerization was prevented by distillation of the monomer at reduced pressure into ether or toluene immersed in a dry ice-alcohol bath. This solution was not allowed to warm up until ready for use in the next step.

TABLE III

PROPERTIES OF α-(2-DIALKYLAMINOETHYL)-4-CHLORO OR METHOXY-1-NAPHTHALENEMETHANOL HYDROCHLORIDES, I

SN	Y	R	YIELD, %[c]	M.P., °C	ANALYSIS			
					Calc'd		Found	
					% C	% H	% C	% H
8744	Cl	C_2H_5[a, b]	33	112.0–113.0	58.96	7.28	58.67	7.36
8738	Cl	C_4H_9	30	147.5–149.0	65.61	8.13	65.63	8.14
8991	CH_3O	C_4H_9[b]	7	121.3–122.8	69.54	9.02	69.65	9.22

[a] This compound was isolated as a monohydrate. A crystalline anhydrous form could not be obtained.

[b] These compounds were shown to be identical, by analysis and mixed m.p., with those prepared by reduction of the corresponding Mannich ketones (1).

[c] This figure represents the yield of pure material.

The Grignard reagents used in this synthesis were 4-methoxy-1-naphthylmagnesium bromide and 4-chloro-1-naphthylmagnesium iodide. The 1-chloro-4-iodonaphthalene required for the latter was conveniently prepared through the chlorination of α-acetamidonaphthalene based on the method of Reverdin and Crepieux (11), with subsequent replacement of the amino group with iodine.

The intermediate chlorohydrins were not isolated in a pure state but were treated directly with the desired dialkylamine. The amino alcohols so produced were isolated and purified as hydrochlorides. Table III lists the properties of these compounds.

EXPERIMENTAL

All melting points are corrected. Analyses were performed by Mr. Jack Ralls and Mr. Bruce Day.

α,α-Dimethyl-β-(di-n-alkylamino)propionaldehydes. These compounds were prepared according to the method of Mannich, Lesser, and Silten (2) for α,α-dimethyl-β-diethylaminopropionaldehyde.

An attempt was made to prepare the 2,4-dinitrophenylhydrazone of the di-*n*-amyl compound by treating 1 ml. of the aldehyde in 50 ml. of 95% ethyl alcohol with 0.7 g. of 2,4-dinitrophenylhydrazine, heating to boiling, adding 3 ml. of concentrated hydrochloric acid, and refluxing for six minutes. On cooling, no crystalline material was obtained. No attempt was made to obtain the free base by neutralizing the reaction mixture.

α-(2-Dialkylamino-tert.-butyl)-4-methoxy-1-naphthalenemethanols. These compounds were all prepared in a completely analogous manner. As an example, the preparation of the hydrochloride of the diethylamino derivative is given.

In a well dried one-l. three-necked flask, kept under slight nitrogen pressure, fitted with a Hershberg stirrer (12), a reflux condenser, and a dropping-funnel were placed 6.0 g. (0.25 g. atom) of magnesium turnings and 50 ml. of anhydrous ether. Then 47.4 g. (0.20 mole) of 1-bromo-4-methoxynaphthalene (5), dissolved in 150 ml. of anhydrous ether and 50 ml. of anhydrous thiophene-free benzene was added dropwise, over the course of ¾ hour, with stirring and refluxing. A small amount of methylmagnesium iodide was added to start the reaction. Refluxing was continued for 3.25 hours longer.

The solution of the Grignard reagent was filtered, under nitrogen, into a one-l. three-necked flask equipped with a Hershberg stirrer, a reflux condenser, and a dropping-funnel. A solution of 23.6 g. (0.15 mole) of α,α-dimethyl-β-diethylaminopropionaldehyde (2) in 80 ml. of anhydrous ether was added dropwise over the course of thirty minutes to the Grignard reagent. A yellow precipitate soon appeared in the flask. The mixture was refluxed and stirred 7.5 hours longer.

The complex was decomposed with ice and saturated ammonium chloride solution. The layers were separated and the aqueous layer was extracted with two 100-ml. portions of ether which were combined with the organic layer, washed twice with saturated ammonium chloride solution, and dried over anhydrous potassium carbonate.

The dry ether solution was treated with an excess of ethereal hydrogen chloride, the ether decanted and the gummy residue taken up in the minimum amount of alcohol. Addition of dry ether caused the product to crystallize. The yield was 37.8 g. (72%) of crude material m.p. 162–164°. Four recrystallizations from alcohol-ether yielded 18.6 g., m.p. 169.0–169.5°. A small sample for analysis was crystallized three more times from alcohol-ether. Tiny, colorless, granular crystals were obtained, m.p. 170.0–170.4°. A dimorphic modification crystallizing in the form of rosettes of tiny needles, m.p. 107.5–109° was also obtained on one occasion.

The isolation and purification of the di-*n*-propyl- and the di-*n*-butyl-amino compounds was almost identical with the above. The hydrochloride of the di-*n*-amyl compound, however, could not be crystallized. The dark red oil resulting from the Grignard reaction was subjected to molecular distillation at 4×10^{-5} mm. pressure and 140–145°. There was obtained 21.7 g. (45%) of an orange-red oil. All attempts to crystallize the hydrochloride of the distilled base failed.

1-Chloro-4-iodonaphthalene. Preparation of 1-amino-4-chloronaphthalene. In a 3-l., three-necked flask fitted with a mechanical stirrer and a condenser attached to a gas trap were placed 243 g. (1.7 moles) of α-naphthylamine (technical), 730 ml. of glacial acetic acid and 174 ml. (188 g., 1.85 moles) of acetic anhydride (technical). The dark purple solution was refluxed for two hours, the reaction mixture cooled in an ice-bath until the temperature reached 35°, and 150 ml. of concentrated hydrochloric acid added. This prevented the α-acetamidonaphthalene from setting to a semi-solid mass. When the temperature reached 21°, 500 ml. more of conc'd hydrochloric acid was added.

With an ice-bath the temperature was kept at 20–24° while a solution of 78.2 g. (0.735 mole) of sodium chlorate in 150 ml. of water was added with stirring over a period of one hour. The mixture was stirred one hour longer in the ice-bath, then two hours at room temperature and left overnight.

The mixture was refluxed for two hours to hydrolyze the amide, the condenser set for distillation and 1100 ml. distilled while 750 ml. of water was added. The reaction mixture was cooled, basified with saturated sodium hydroxide, and allowed to cool overnight after removal of the stirrer.

The product, which had settled as a black oil and solidified, was transferred to a 500-ml. Claisen flask and distilled with superheated steam (the temperature of the issuing vapors being 130–135°) until the organic phase almost stopped distilling (about six hours). The product, which had distilled as a light purple oil and solidified in the receiver was air dried.

The yield of crude 1-amino-4-chloronaphthalene was 155 g. (51%). This was crystallized once from hexane (Skellysolve B, b.p. 60–70°) and yielded 106 g. (35%), m.p. 95–97°. This material was pure enough for the next step.

Diazotization of the amino group and replacement with iodine. In a 2-l., three-necked flask fitted with a mechanical stirrer, dropping-funnel, and thermometer, were placed 65.5 g. (0.369 mole) of 1-amino-4-chloronaphthalene and a solution of 31 ml. of concentrated sulfuric acid in 1000 ml. of water. The mixture was cooled to 0° and a solution of 27.4 g. (0.385 mole) of sodium nitrite (97%) in 80 ml. of water was added over a two-hour period, the temperature being kept below 5°. The mixture was allowed to stand in the ice-bath for a half hour, filtered quickly through glass wool and added cautiously to a solution of 90 g. (0.54 mole) of potassium iodide in 100 ml. of water in a 4-l. beaker fitted with a mechanical stirrer. The reaction mixture foamed very badly.

After about one hour, most of the reaction was over. The reaction mixture was stirred one hour longer, then heated until the black product melted and settled to the bottom. On cooling, the black oil solidified and was removed and air dried. This material was extracted three times with 500-ml. portions of boiling methanol and a black tarry residue was discarded. The methanol solution was decolorized with Nuchar until light yellow, and the product was crystallized by concentration. The yield of light yellow 1-chloro-4-iodonaphthalene was 72 g. (68% based on 1-amino-4-chloronaphthalene), m.p. 52.5–53.8°. Beattie and Whitmore (13) report m.p. 54.5°.

Several other syntheses of 1-chloro-4-iodonaphthalene were investigated but the above is in our opinion the best. Although the method of Beattie and Whitmore (13) gave a higher over-all yield (39% from sodium naphthionate), it was tedious, and the intermediate mercury compound produced an unpleasant skin rash. The nitration of α-chloronaphthalene to yield 1-chloro-4-nitronaphthalene, which could be readily reduced to 1-amino-4-chloronaphthalene, was attempted by the method of Ferrero and Caflisch (14). The desired compound could only be obtained in very low yield. The method reported by Pajak (15) of treating α-naphthylhydroxylamine with concentrated hydrochloric acid to yield 1-amino-4-chloronaphthalene could not be repeated. We have prepared 1-chloro-4-iodonaphthalene in 31% over-all yield (based on 1-aceto-4-chloronaphthalene), by preparing 1-amino-4-chloro-naphthalene by a Beckmann rearrangement of methyl 4-chloro-1-naphthyl ketoxime (16).

α-(2-Diethylaminoethyl)-4-chloro-1-naphthalenemethanol hydrochloride. Preparation of β-chloropropionaldehyde. In a 50-ml. flask in an ice-salt bath at −10° was placed 14.5 ml. (12.1 g., 0.216 mole) of redistilled acrolein. Dry hydrogen chloride gas was passed over the acrolein with occasional swirling. When 7.6 g. (96% theory) had been taken up, the contents of the flask were transferred to a 50-ml. modified Claisen flask with the aid of a little ether, and a few crystals of hydroquinone and *p*-toluenesulfonic acid were added.

The mixture was distilled under nitrogen at 20 mm. in an oil-bath at 75° until the distillate was one phase (no more water distilling). The distillate was about 4 ml. The receiver was then changed to a tared 125 ml. distilling flask containing 75 ml. of absolute ether, which had been weighed and immersed in a dry ice-alcohol bath; the distillation was then continued until the distillate practically stopped coming over. The increase in weight of the receiver was 8.3 g. (0.090 mole, 43% yield assuming the weight increase to be pure β-chloropropionaldehyde). The solution was left immersed in the dry ice-alcohol bath while the Grignard reagent was being prepared.

Reaction of β-chloropropionaldehyde with 4-chloro-1-naphthylmagnesium iodide. In a 500-ml. three-necked flask fitted with a reflux condenser, a dropping-funnel and a mechanical stirrer were placed 28.9 g. (0.10 mole) of 1-chloro-4-iodonaphthalene, 150 ml. of absolute ether, and 2.3 g. (0.095 mole) of magnesium turnings. The reaction started immediately and the mixture was refluxed until all the magnesium had reacted.

The ethereal aldehyde solution was warmed to about 10° and added to the Grignard solution dropwise at a rate to maintain refluxing; after one hour of further refluxing the solution was cooled in ice and hydrolyzed with 40 ml. of 3 *N* sulfuric acid. The ether solution was separated, washed, and dried.

Condensation of the chlorohydrin with diethylamine. The solvent was removed from the above solution at reduced pressure, the light-colored oil taken up in 100 ml. of acetone and 22 ml. (15.5 g., 0.21 mole) of diethylamine and 7.5 g. (0.05 mole) of sodium iodide added. The solution was refluxed seventeen hours.

The reaction mixture was transferred to a 500-ml. Claisen flask with 200 ml. of 3 *N* sodium hydroxide solution and distilled at 140 mm. pressure, under nitrogen, until there was no odor of diethylamine in the distillate. The residual dark oil was taken up in ether, washed, and dried.

The addition of excess ethereal hydrogen chloride to the ether solution precipitated a brown taffy. This material was treated with 50 ml. of boiling ethyl acetate and absolute ethanol was added until all was in solution. On cooling, the solution deposited 5.5 g. of nearly colorless product, m.p. 112–114°. Concentration of the mother liquor produced 5.5 g., m.p. 103–108°, which was recrystallized from ethyl acetate-ethanol to yield 4.2 g., m.p. 112–113°. The total yield was 9.7 g. (33%, based on β-chloropropionaldehyde).

α-(2-Dibutylaminoethyl)-4-chloro-1-naphthalenemethanol hydrochloride was prepared in a completely analogous manner.

α-(2-Dibutylaminoethyl)-4-methoxy-1-naphthalenemethanol hydrochloride. By a procedure similar to that used for the above 4-chloro compounds, 4-methoxy-1-naphthylmagnesium bromide was treated with β-chloropropionaldehyde (in toluene) and the crude chlorohydrin was treated with di-*n*-butylamine. The crude product was subjected to molecular distillation at 5×10^{-5} mm. pressure and after a forerun of α-methoxynaphthalene (excess Grignard used) there was obtained a fraction of crude base from which was obtained 4.4 g. (7%) of the product desired.

SUMMARY

Four α-(2-dialkylamino-*tert.*-butyl)-4-methoxy-1-naphthalenemethanols were prepared by the reaction of 4-methoxy-1-naphthylmagnesium bromide and α,α-dimethyl-β-dialkylaminopropionaldehydes. The aldehydes were prepared by the Mannich reaction.

The reaction of β-chloropropionaldehyde with 4-methoxy- or 4-chloro-1-naphthylmagnesium bromide gave chlorohydrins which were readily converted into α-(2-dialkylaminoethyl)-4-chloro- or -methoxy-1-naphthalenemethanols.

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