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

SUBSTITUTED α-DIALKYLAMINOALKYL-1-NAPHTHALENE-METHANOLS. IX. α-(2-DIALKYLAMINOETHYL)-α-METHYL ARYLMETHANOLS[1]

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Because of the availability of 1-dialkylamino-3-butanones through the Mannich synthesis, compounds of the type aryl-$C(CH_3)(OH)CH_2CH_2NR_2$ should readily be prepared by a Grignard reaction as shown in the following equations:

$$CH_3COCH_3 + R_2NH_2Cl + (CH_2O) \rightarrow CH_3COCH_2CH_2NR_2$$

$$\text{Aryl—MgX} + CH_3COCH_2CH_2NR_2 \rightarrow \text{Aryl—}\overset{\displaystyle CH_3}{\underset{\displaystyle OH}{\overset{|}{\underset{|}{C}}}}CH_2CH_2NR_2$$

These compounds were of interest as possible antimalarials.

At the time this work was started, only two references (1, 2) were found to the reaction of β-amino ketones with Grignard reagents. In 1944 Cromwell and Burch (3) reported moderate yields in a similar reaction. The reaction of the Grignard reagent with several β-amino esters and aldehydes has also been reported (4, 5, 6, 7).

We found that pure amino alcohols could be isolated in only 15–33% yields from the reaction of 1-dialkylamino-3-butanones with aryl Grignard reagents. The products were difficult to purify and often formed oily salts even when pure. The desired reaction was accompanied by a side reaction which gave dialkylamine and the product of simple hydrolysis of the Grignard reagent. Such a reaction is readily formulated as follows:

$$CH_3COCH_2CH_2NR_2 + \text{Aryl-MgX} \rightarrow CH_3COCH{=}CH_2 + \text{Aryl-H} + R_2NMgX$$

If methyl vinyl ketone were produced it would be expected to react with the Grignard reagent or polymerize. Smith and Sprung (8) observed that the reaction of methyl vinyl ketone with laurylmagnesium bromide went poorly, the ketone polymerizing, but Heilbron and co-workers (9) found that hexynylmagnesium bromide gave a 55% yield of the 1,2-addition product with that ketone. We found that the products of the reaction between phenyl- or naphthyl-magnesium bromide and 1-dialkylamino-3-butanones contained no unsaturated substances, but time did not permit a close search for other products.

[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.

A preliminary study of the reaction of 1-dialkylamino-3-butanones with methylmagnesium iodide in the Grignard machine (10, 11) revealed that 0.9 to 0.95 mole of methane was produced per mole of ketone. A further 0.25 to 0.35 mole of methylmagnesium iodide was used up in an addition reaction. On the basis of the above side reaction, this addition would be expected to be greater. The small amount of addition is consistent with the idea that the Grignard reagent has an enolizing action on Mannich ketones. Enolization was suggested

TABLE I

α-(2-DIALKYLAMINOETHYL)-α-METHYL ARYLMETHANOLS, $\mathrm{ARYL\text{-}C(CH_3)(OH)CH_2CH_2NR_2}$

SN	ARYL GROUP	R	M.P., °C.[b]	SOLUBILITY[a]	ANALYSES[b]			
					C		H	
					Calc'd	Found	Calc'd	Found
8349	Phenyl	Ethyl	141–142.5	>100	65.22	65.18	9.38	9.30
	1-Naphthyl	Ethyl	96.5–98[d]	21[d]	66.34[d]	66.32	8.66	8.68
	1-Naphthyl	*n*-Butyl	170.5–171.5	0.9	72.60	72.56	9.42	9.44
	2-Naphthyl	Ethyl	145–154[e]	>40	70.22	70.07	8.51	8.57
5903	4-Methoxy-1-naphthyl	Methyl	103–103.5[c] 195–210 dec.	Very sol.	74.69[e]	74.49	8.48	8.47
6977	4-Methoxy-1-naphthyl	Ethyl	182–182.5	7	67.54	67.36	8.35	8.38
6760	4-Methoxy-1-naphthyl	*n*-Butyl	137–138[f]	1.5	70.11	70.23	9.21	9.31
	9-Phenanthryl	Ethyl	181–186	>10	73.82	73.22 73.27	7.88	8.11 7.94
6937	9-Phenanthryl	*n*-Butyl	76.5–77[c]	8[g]	82.70[c]	83.00	9.34	9.34

[a] Solubility of hydrochloride at 25° in water; g./100 ml. of solution.
[b] Data for the hydrochloride except where indicated.
[c] Free amine.
[d] Hydrochloride monohydrate.
[e] Broad m.p. believed due to existence of 2 crystalline forms.
[f] Needles. This compound also crystallized in plates, m.p. 133–134°.
[g] Solubility of free base in 0.2 *N* hydrochloric acid.

by Wiley and Adkins (12) to explain their observation that 1-amino-2-alkyl-4-methyl-3-pentanones gave two moles of methane and no addition in the Grignard machine.

The course of the reaction between Mannich ketones and the Grignard reagent is under further investigation and will be reported later.

Table I lists the amino alcohols which were prepared for testing as antimalarials. Three of the products were not obtained as crystalline solids either as free amines or salts, and are not included in the table. These were α-(2-di-*n*-propylaminoethyl)-α-methyl-4-methoxy-1-naphthalenemethanol, α-(2-diethyl-

aminoethyl)-α-methyl-4-chloro-1-naphthalenemethanol and the corresponding di-*n*-butylamino compound.

Several other methods for the preparation of α-(2-dialkylaminoethyl)-α-methyl arylmethanols were tried. The reaction of 1-dialkylamino-3-butanones with arylcadmium compounds gave only amorphous products, and with aryllithium compounds the yields of amino alcohol were lower than with the Grignard reagent. An unsuccessful attempt was made to obtain α-(2-dibutylaminoethyl)-α-methyl-4-methoxy-1-naphthalenemethanol by the reaction of 2-dibutylaminoethyl 4-methoxy-1-naphthyl ketone and methylmagnesium iodide. A second synthesis was found which involved the preparation of β-bromoethyl methyl ketone, its reaction with 4-methoxy-1-naphthylmagnesium bromide and treatment of the product with dibutylamine. The resulting compound was identical with that obtained from 1-dibutylamino-3-butanone and 4-methoxy-1-naphthylmagnesium bromide. A few examples of similar syntheses have been reported (7, 13, 14).

Further work on the series was not undertaken because the results of avian testing indicated that the compounds were poor antimalarials.

EXPERIMENTAL

All melting points are corrected unless marked otherwise. Analyses were carried out by Bruce F. Day, Richard Nevé and Jack W. Ralls.

1-Dialkylamino-3-butanones. The procedure of Wilds and Shunk (15) for the Mannich reaction was used with only slight modification. It was found that 0.5 to 1.5 ml. of hydrochloric acid improved the yield and shortened the reflux time in the condensation of acetone and paraformaldehyde with dimethylamine, di-*n*-propylamine, and di-*n*-butylamine. The addition of hydrochloric acid in the Mannich condensation has been suggested before (16). With diethylamine this procedure increased the yield of 1,1-bis-(diethylaminomethyl)acetone and polymeric products at the expense of the compound desired. For the synthesis of 1-diethylamino-3-butanone we followed exactly the procedure of Wilds and Shunk and checked the data they reported.

1-Dimethylamino-3-butanone (17). Reflux time, three hours; yield, 45%; b.p., 70°/40 mm.; n_D^{25} 1.4213; d_4^{25} 0.8636; MR_D obs. 33.84, Calc'd 33.86.

Anal. Calc'd for $C_6H_{13}NO$: C, 62.62; H, 11.31.
Found: C, 62.49; H, 11.28.

1-Di-n-propylamino-3-butanone. Reflux time, four hours; yield, 66%; b.p. 116–117°/11 mm.; n_D^{25} 1.4331; d_4^{25} 0.8498; MR_D obs. 52.39, Calc'd 52.33.

Anal. Calc'd for $C_{10}H_{21}NO$: C 70.12; H, 12.36.
Found: C, 70.16; H, 12.32.

1-Di-n-butylamino-3-butanone. Reflux time, four hours; yield, 62%; b.p. 80°/2 mm.; n_D^{25} 1.4381; d_4^{25} 0.8466; MR obs. 61.82, Calc'd 61.57.

Anal. Calc'd for $C_{12}H_{25}NO$: C, 72.30; H, 12.64.
Found: C, 72.38; H, 12.68.

Grignard reagents. The use of benzene as an accessory solvent was necessary for all of the Grignard reagents except phenylmagnesium bromide. β-Bromonaphthalene was obtained from β-naphthylamine, and 9-bromophenanthrene from purified phenanthrene (18) by slight modification of known methods (19, 20). The 4-chloro-1-iodonaphthalene used in this work was prepared by the method of Beattie and Whitmore (21) although a less tedious method was found later (7). Carbonation of the Grignard reagent from this compound gave 4-chloro-1-naphthoic acid, m.p. 221–223°, neutral equivalent 208.1 (Calc'd 206.6). The acid contained no iodine and gave no melting point depression when mixed with the acid prepared by hypochlorite oxidation of 4-chloro-1-acetonaphthone (22).

4-Bromo-1-methoxynaphthalene. The bromination of 1-methoxynaphthalene was carried out with iodine monobromide by Militzer's method (23) using chloroform as the extracting solvent. The product was an oil, b.p. 147–153° 3 mm. on the second distillation, yield 75%, $n_D^{21.5}$ 1.6532. 4-Bromo-1-methoxynaphthalene has been reported three times in the literature with the following constants: b.p. 181° 18 mm. (24), b.p. 178° 15 mm. (25), and m.p. 46° (26). Our product could be induced to crystallize at −80°, but melted below room temperature. An attempt to obtain a solid product by repetition of the procedure of Underwood, Baril, and Toone (26) was unsuccessful. The structure of the 4-bromo-1-methoxynaphthalene obtained using iodine monobromide was proved by carbonation of its Grignard reagent. 4-Methoxy-1-naphthoic acid was obtained in 84% yield, m.p. 242–243° (from alcohol).

Anal. Calc'd for $C_{12}H_{10}O_3$: C, 71.28; H, 4.99, neutral equivalent 202.2.
Found: C, 70.82; H, 5.01, neutral equivalent 197.

The following melting points have been reported for 4-methoxy-1-naphthoic acid: 239° (27), 232° and 230° (29). No other known 1-methoxynaphthoic acid has a melting point near this value; 1-methoxy-6-naphthoic acid has not been reported.

α-(2-Dialkylaminoethyl)-α-methyl arylmethanols. The general procedure used for the condensation of aryl Grignard reagents with 1-dialkylamino-3-butanones is illustrated by the directions for α-(2-di-*n*-butylaminoethyl)-α-methyl-1-naphthalenemethanol.

A solution of α-naphthylmagnesium bromide prepared from 41.5 g. (0.2 mole) of α-bromonaphthalene in 185 ml. of ether and 50 ml. of benzene was filtered into a 1-liter, 3-n. flask equipped with a mercury-sealed stirrer, reflux condenser, and dropping-funnel. This solution was cooled in an ice-bath and stirred under nitrogen while a solution of 40 g. (0.2 mole) of 1-di-*n*-butylamino-3-butanone in 100 ml. of ether was added dropwise during thirty minutes. The mixture was refluxed with stirring for one hour, then cooled in ice during the addition of 100 ml. of saturated ammonium chloride solution. The aqueous layer was separated and washed twice with small portions of ether which were combined with the ether-benzene layer; the latter was extracted three times with 100 ml. portions of 2 *N* hydrochloric acid. A light colored, crystalline solid soon separated from this acid solution; it was collected after standing at 0° for several hours and washed on the filter with a little ice-water. The yield of light yellow solid, m.p. 161–166.5°, was 21 g. (29%). Recrystallization from alcohol-ether and from water gave white plates of pure α-(2-di-*n*-butylaminoethyl)-α-methyl-1-naphthalenemethanol hydrochloride (Table I).

The acid solution gave no more solid on concentration to 100 ml. under reduced pressure; it was basified with 6 *N* sodium hydroxide in an ice-bath and saturated with potassium carbonate. The oil that separated was taken up in ether, dried over potassium carbonate, and the solution concentrated at reduced pressure (residue 18 g.). This residue was held at 70° under 3 mm. pressure for seven hours and the distillate was collected in a trap cooled in dry ice. Di-*n*-butylamine was isolated from the condensate as the hydrochloride (7.8 g.; 0.047 mole), identified by reaction with phenyl isothiocyanate to give N-phenyl-N,N-di-*n*-butylthiourea, m.p. and mixed m.p. 83–84°. The basic material which did not distill could not be induced to crystallize or to yield a solid salt.

The ether-benzene solution from the original reaction mixture did not contain unsaturated compounds. From it was isolated by sublimation 14 g. (0.11 mole) of naphthalene.

A crystalline hydrochloride separated from the hydrochloric acid extract only in the case of α-(2-di-*n*-butylaminoethyl)-α-methyl-1-naphthalenemethanol. In all other cases, the free base was liberated from the hydrochloric acid solution by basifying with dil. sodium hydroxide in the cold. The amino alcohol was taken up in ether, the ether solution dried over potassium carbonate, and the hydrochloride formed by passing anhydrous hydrogen chloride over the surface of the cold solution with swirling. Excess hydrogen chloride caused oil formation and even when a solid was obtained, it often turned oily when filtered (possibly it was an etherate). Sometimes these oily hydrochlorides solidified on long standing. It was occasionally preferable to remove ether from the dried solution of amino alcohol, dissolve the residue in anhydrous ethanol, saturate the solution with anhydrous

hydrogen chloride, and precipitate the hydrochloride by adding ether. Another effective procedure was fractional extraction of the original ether-benzene solution with small portions of 0.5 *N* hydrochloric acid. An impurity (probably dialkylamine hydrochloride) was taken up first, and later fractions gave solid hydrochlorides. Hydrobromides, sulfates, oxalates, and other salts usually behaved like the hydrochlorides.

Hydrochlorides were crystallized from anh. alcohol, ethyl acetate, or chloroform by adding anh. ether or occasionally petroleum ether. The free bases were crystallized from acetone and water.

α-(2-Di-n-butylaminoethyl)-α-methyl-4-methoxy-1-naphthalenemethanol. This compound was obtained in 27% yield by the synthesis described above. It was also prepared from β-bromoethyl methyl ketone (30) and 4-methoxy-1-bromonaphthalene by a synthesis which was tried only once. β-Bromoethyl methyl ketone was obtained from β-bromopropionyl chloride and dimethylcadmium following the general directions of Gilman and Nelson (31). The acid chloride was readily prepared from β-bromopropionic acid (32) and thionyl chloride. β-Bromoethyl methyl ketone was an unstable liquid which decomposed on attempted distillation at 3 mm. The homologous β-bromoethyl ethyl ketone is also an unstable liquid (13). The crude methyl ketone was dried in ether and added to a slight excess of 4-methoxy-1-naphthylmagnesium bromide to yield α-(2-bromoethyl)-α-methyl-4-methoxy-1-naphthalenemethanol which was isolated but not purified. It was converted to the desired amino alcohol by heating in a sealed tube at 120–130° for twenty-four hours with slightly more than two moles of di-*n*-butylamine.

SUMMARY

Nine α-(2-dialkylaminoethyl)-α-methyl arylmethanols have been prepared by the reaction of aryl Grignard reagents with 1-dialkylamino-3-butanones. Yields of only 15–33% were obtained due to side reactions and to difficulties in purification of the final products.

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