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

SUBSTITUTED α-DIALKYLAMINOALKYL-1-NAPHTHALENE-METHANOLS. VI. SOME MANNICH KETONES AND DERIVED PROPANOLAMINES[1]

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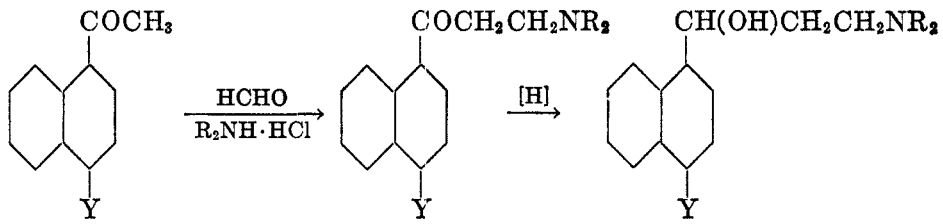
In the search for antimalarial drugs, the group at the National Institute of Health has investigated as well as ethanolamines, the amino alcohols of type III with the propanolamine side chain. At the suggestion of Dr. Lyndon F. Small, we undertook the preparation of the propanolamines in which the naphthalene nucleus was substituted with a methoxyl group or a halogen atom just as we did in the case of the ethanolamines (1).



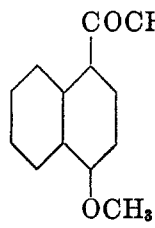
I II III

The most direct approach to compounds of the type III is, of course, through the Mannich ketones II. This is the method used at the National Institute of Health, and the one we used for the preparation of several propanolamines. Our preparations in this connection and some observations on the Mannich reaction are reported in this paper. In certain cases, sometimes for interesting reasons, the preparation by way of the Mannich ketones proved impossible, and a number of propanolamines were prepared by other methods discussed in the following article (2).

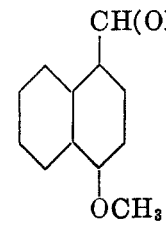
In the course of our work we prepared Mannich ketones II from 4-methoxy- and 4-chloro-1-acetonaphthone and several dialkylamines (Table I). In these preparations nitromethane possessed advantages over several more conventional (3) solvents and is recommended for trial in other cases.

In attempting to prepare an amino ketone from 4-methoxy-1-isobutyronaphthone IV in order to arrive eventually at a branched chain amino alcohol V,

[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.



IV



V

we came across an interesting structural limitation of the Mannich reaction. The isobutyronaphthone was recovered unchanged even when conditions were very vigorous. Similarly, isobutyrophenone survived the conditions of the

TABLE I

AMINO KETONES $YC_{10}H_6COCH_2CH_2NR_2 \cdot HCl$ FROM SUBSTITUTED 1-ACETONAPHTHONES

Y	R	YIELD, %	M.P., °C	ANALYSIS			
				Calc'd		Found	
				% C	% H	% C	% H
4-OCH_3	CH_3	44	172.7–173.7	65.41	6.86	65.79	6.96
4-OCH_3	C_2H_5	63	105.3–106.3[a]	63.61	7.71	63.43	7.62
			152.3–152.8[b]	67.17	7.52	66.83	7.59
4-OCH_3	n-C_4H_9	69	137.5–139.0	69.91	8.54	69.87	8.59
4-OCH_3	n-C_5H_{11}	74	126.0–126.5	71.00	8.94	71.10	8.89
4-Cl	CH_3	64	155–156.5	60.41	5.75	60.28	5.74
4-Cl	C_2H_5	70	128–129	62.58	6.49	62.31	6.49
4-Cl	n-C_4H_9	60	131–132	65.96	7.64	65.70	7.75

[a] Monohydrate.

[b] Anhydrous.

Mannich reaction. Methyl aryl ketones undergo the Mannich reaction smoothly as demonstrated by this and considerable earlier work (3). A substance such as 4-methoxypropiophenone with one more carbon atom in the side chain undergoes the Mannich reaction smoothly, although there is evidence that the reaction is a little slower than for 4-methoxyacetophenone (4). However, there is apparently a much more marked effect of the second methyl group when one goes to the branched chain aryl ketones.

The branched chain isobutyraldehyde is known to undergo the Mannich reaction smoothly (2, 5) and we thought it worth while to try diisopropyl ketone in this reaction. As expected, this carbonyl compound seemed to fall in a position intermediate between isobutyraldehyde and the branched chain aryl ketones. Judging by the equivalent weight and nitrogen analysis, the product contained an 8% yield of the Mannich ketone VI and a 12% yield of the di-dialkylaminomethane VII from the formaldehyde and dibutylamine. The mixed product yielded formaldehyde dinitrophenylhydrazone from an acidic medium.

$(CH_3)_2CHCOC(CH_3)_2CH_2N(C_4H_9)_2$

VI

$(C_4H_9)_2NCH_2N(C_4H_9)_2$

VII

A satisfactory explanation of the behavior of the branched chain aryl ketones in attempts to carry out the Mannich reaction must await further evidence on the mechanism of the reaction. This evidence we hope to produce when time permits. However, it is interesting to notice the behavior of isobutyrophenone in other reactions involving the *alpha* hydrogen atom. For example, this ketone is halogenated satisfactorily, the rate of acid-catalyzed halogenation being slower than the one for acetophenone by a factor of approximately fifty in the case of iodination in aqueous perchloric acid solution (6) and approximately ten in the case of bromination in an acetic acid solution of hydrochloric acid (7). On the other hand, isobutyrophenone appears not to condense with ethyl phthalate with sodium ethoxide as a catalyst (8). Most interesting in connection with our work is the observation that isobutyrophenone reacts with formaldehyde by a complex process which must, however, involve condensation with the formaldehyde (9).

The amino alcohols (Table II) which we prepared as possible antimalarials were derived by reduction of the Mannich ketones II. Catalytic hydrogenation

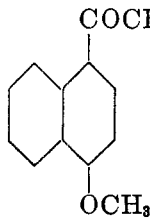
TABLE II

AMINO ALCOHOLS $YC_{10}H_6\ CHOHCH_2CH_2NR_2 \cdot HCl$

SN	Y	R	M.P., °C	YIELD, %	ANALYSIS	
					Calc'd	Found
					% C % H	% C % H
8991	4-OCH_3	*n*-C_4H_9	125.8–127.8	52	69.54 9.02	69.61 9.27
10200	4-OCH_3	*n*-C_5H_{11}	117.7–118.7	53	70.65 9.39	70.31 9.49
8744	4-Cl	C_2H_5[a]	112–114	8	58.96 7.28	59.06 7.51

[a] Monohydrate.

of the 4-methoxyamino ketone hydrochlorides using Adams' catalyst gave rise to fair yields of the products together with some of the hydrogenolysis product, 4-methoxy-1-propionaphthone VIII. When Raney nickel or palladium catalysts were used only hydrogenolysis occurred. When the free amino ketone was subjected to hydrogenation, only hydrogenolysis occurred in line with the greater tendency toward this cleavage displayed by free β-amino ketones over the corresponding salts (10). It is of some interest in connection with the mechanism of the hydrogenolysis that the free Mannich base IX from isobutyraldehyde and dipropylamine, which we describe in another article (2), is hydrogenated with Adams' catalyst in quantitative yield to the neopentyl alcohol X.



VIII

$(n\text{-}C_3H_7)_2NCH_2C(CH_3)_2CHO$

IX

$(n\text{-}C_3H_7)_2NCH_2C(CH_3)_2CH_2OH$

X

Catalytic hydrogenation of the 4-chlorodibutylamino ketone hydrochloride with Adams' catalyst gave a large proportion of cleavage of the nuclear halogen and was therefore unsuccessful. Although the nuclear halogen-substituted amino alcohols were best prepared by another method reported elsewhere (2), we did prepare one of them in poor yield by aluminum isopropoxide reduction of the Mannich ketone. We found as Fry (11) did in similar cases that somewhat better yields were obtained with the hydriodide. The aluminum isopropoxide reduction did not succeed with the 4-methoxydibutylamino ketone II (Y = OCH_3; R = n-C_4H_9). Neither did the use of sodium amalgam in acid solution or isobutylmagnesium bromide give anything but uncharacterized oils.

Reduction of a 4-methoxyamino ketone II (Y = OCH_3; R = n-C_4H_9) with activated aluminum gave rise to two diastereomeric glycols XI (SN-9860). This behavior is common with arylamino ketones (4, 12).

$$\begin{matrix} CH_3OC_{10}H_6C(OH)CH_2CH_2N(C_4H_9)_2 \\ | \\ CH_3OC_{10}H_6C(OH)CH_2CH_2N(C_4H_9)_2 \end{matrix}$$

XI

EXPERIMENTAL

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

Mannich reactions with 1-acetonaphthones. The best procedure used nitromethane as a solvent and is illustrated in detail for the preparation of 4-methoxy-1-(β-diethylaminopropio)naphthone.

In a 250-ml., three-necked flask equipped with a thermometer, a Hershberg stirrer (13) and a reflux condenser attached through a gravity type water separator, were placed 20.0 g. (0.10 mole) of 1-aceto-4-methoxynaphthone (1), 11.0 g. (0.10 mole) of diethylammonium chloride, 4.5 g. (0.15 mole) of paraformaldehyde, 0.23 ml. of conc'd hydrochloric acid, 35 ml. of nitromethane, 5 ml. of absolute alcohol, and 10 ml. of toluene. The mixture was stirred and refluxed for one-half hour during which the inside temperature rose from 92° to 93° and 2.1 ml. of water was collected in the separator. The mixture was poured into a flask, allowed to cool, and diluted to about 300 ml. with anhydrous ether. The solution was stored overnight in the refrigerator. The crystallized product was filtered, washed on the filter several times with water and dried over phosphorus pentoxide. Further dilution of the mother liquors with ether brought the total yield of material to 21.4 g. (63%). One recrystallization from a mixture of acetone and absolute alcohol yielded 19.1 g. (56%) of material, m.p. 105.3–106.3°, which proved to be a monohydrate. Storage *in vacuo* over phosphorus pentoxide for a week converted the hydrate to a white hygroscopic powder, m.p. 152.3–152.8°, which had the composition of the anhydrous amino ketone hydrochloride.

A procedure similar to the above was also used with the dibutyl and the diamyl analogs from 4-methoxy-1-acetonaphthone. The crude yields were 69 and 74% respectively, the yields of pure material, 62 and 60%.

The Mannich reaction involving 4-methoxy-1-acetonaphthone and diethylammonium chloride was also carried out in nitrobenzene-benzene as a solvent, as suggested to us by Dr. E. M. Fry (11, 14). The proportions of materials were the same as those above except that the solvent contained 2 ml. of absolute alcohol, 24 ml. of nitrobenzene, and 24 ml. of benzene. After the proper reflux period, the reaction mixture was worked up in a manner which differed in some details from the procedure outlined above. The yields varied markedly with the length of the reflux period, a one-hour period giving a crude yield of 55%, a two-hour period 47% and a three-hour period 29%. These results parallel those of Fry (14) in similar cases.

For the Mannich reaction with 4-methoxy-1-acetonaphthone and dimethylammonium chloride, isoamyl alcohol was used for the solvent. The materials employed consisted of 0.05 ml. conc'd hydrochloric acid, 2.78 g. (0.034 mole) of dimethylammonium chloride, 1.02 g. (0.034 mole) of paraformaldehyde, 6.8 g. (0.034 mole) of 4-methoxy-1-acetonaphthone, and 16 ml. of absolute isoamyl alcohol. A 5.5-hour reflux period was allowed. The reaction mixture was cooled in the refrigerator and the product filtered and washed with cold isoamyl alcohol. Dilution of the mother liquors with cold ether gave enough additional product to bring the total crude yield to 44%. Purification was effected by conversion to free base, reprecipitation of the hydrochloride from anhydrous ether by the addition of ethereal hydrogen chloride, and recrystallization of the hydrochloride from alcohol-ether. A similar procedure was used for the Mannich reaction with 4-chloro-1-acetonaphthone and dimethylammonium chloride. A two-hour reflux period was allowed and the product was purified by crystallization from ethanol. The yield was 64%.

The Mannich ketones from 4-chloro-1-acetonaphthone and diethyl- and di-*n*-butylammonium chloride were prepared in nitromethane as described above. The di-*n*-butylamino ketone was purified by washing with water and recrystallizing from ethyl acetate, yield 60%. With the diethyl analog it was necessary to convert to the free base and steam distill at water-pump pressure to remove diethylamine. The base was then reconverted to the hydrochloride. Further purification was unnecessary; yield 70%.

1-Isobutyro-4-methoxynaphthone. This material was prepared similarly to 4-methoxy-1-acetonaphthone (1) from isobutyryl chloride, α-methoxynaphthalene and aluminum chloride in carbon disulfide. There was obtained after two recrystallizations from ligroin, b.p. 60–70°, a 72% yield of pale yellow prisms, m.p. 96–98° (m.p. after three more crystallizations 97.0–97.5°).

Anal. Calc'd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06.
Found: C, 78.95; H, 6.90.

A sample of this material was oxidized with potassium ferricyanide (15) at 65° for 95 hours. The product was recrystallized from alcohol to yield 40% of the theoretical amount of 4-methoxy-1-naphthoic acid, m.p. 237–239° (uncorr.). No depression was observed on admixture with material prepared in this laboratory (16) by carbonation of the Grignard reagent from 4-methoxy-1-bromonaphthalene.

Attempted Mannich reactions with 1-isobutyro-4-methoxynaphthone and isobutyrophenone. Di-*n*-butylammonium chloride was used in these attempts. The reaction was tried in nitromethane in a manner similar to that used with 1-aceto-4-methoxynaphthone. With the 1-isobutyro-4-methoxynaphthone, after a one-hour reflux period, the cooled solution was diluted with anhydrous ether and stored in the ice chest. Only di-*n*-butylammonium chloride was obtained. This was filtered and from the filtrate, after suitable purification, there was isolated 76% of unreacted ketone.

Other attempts gave a 92% recovery of naphthone after a 12-hour reaction period in nitromethane, an 88% recovery after a 2.5-hour reflux period in 1-nitropropane, and a 91% recovery after a 3.5-hour reflux period in isoamyl alcohol.

With isobutyrophenone (17) after a 1.25-hour reflux period, there were obtained an 84% recovery of dibutylammonium chloride and a 78% recovery of isobutyrophenone, m.p. and mixed m.p. of 2,4-dinitrophenylhydrazone 163–164° (7). Hold-up and still bottoms in the distillation of isobutyrophenone added an estimated 13% to the recovery.

The Mannich reaction with diisopropyl ketone. Di-*n*-butylammonium chloride was used in this reaction and the procedure was similar to that of Mannich (5). The diisopropyl ketone was kindly supplied by Dr. J. D. Roberts of this laboratory. After a 3.25-hour refluxing period, the cooled reaction mixture was poured into water and the organic layer separated. The aqueous layer was made alkaline and extracted with ether. The solvent was evaporated after drying and the residue was distilled *in vacuo*. Several cuts were taken but no pure material was obtained and the largest fraction was redistilled. The two main fractions still possessed a wide boiling range and they were combined and redistilled. At 3 mm. the main fraction, 5.2 g. (20%), had the following properties: b.p. 112–114° (3 mm.), n_D^{20} 1.4437.

Anal. Calc'd for $C_{16}H_{33}NO$: C, 75.23; H, 13.02; N, 5.48.
Calc'd for $C_{17}H_{35}N_2$: C, 75.48; H, 14.16; N, 10.36.
Found: C, 75.24; H, 13.71; N, 8.59.

The equivalent weight of this fraction was obtained by titration with acid to the methyl red end-point.

Equiv. Wt. Calc'd for $C_{16}H_{33}NO$: 255.
Calc'd for $C_{17}H_{38}N_2$: 135.
Found: 166, 168, 169.

When the 2,4-dinitrophenylhydrazone of this fraction was prepared in alcohol containing hydrochloric acid, the only product obtained was formaldehyde 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 164.8–165.3°. This fraction gave a silver mirror when warmed with ammoniacal silver nitrate.

The ready production of formaldehyde in acid solution from compounds of the type VII is well known (18). As a control, we treated the Mannich base from isobutyraldehyde and diamylamine (2) in acid solution with dinitrophenylhydrazine. No hydrazone was precipitated.

Hydrogenation of amino ketones over Adams' catalyst. The reactions were carried out at atmospheric pressure and were interrupted at about 100% absorption. In the case of the 4-methoxydibutylamino ketone hydrochloride, the reaction mixture was filtered and the solution was concentrated under reduced pressure. The resulting syrup was triturated with dry ether and the solid collected on a filter, washed with ether, and dried. The combined filtrate and washings on evaporation gave a green oil which, on crystallization from methanol, yielded 22% of 4-methoxy-1-propionaphthone, m.p. 56–57° [literature: 57°, 58° (19)], m.p. of oxime 172–174° [literature: 172° (19c)].

Anal. Calc'd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59.
Found: C, 73.33; H, 6.60.

The crude solid from above was washed on the funnel with water. From the water washings there was obtained 20% of di-*n*-butylammonium chloride identified through the phenylthiourea derivative. The crude amino alcohol hydrochloride (52%), m.p. 124–126°, on the funnel was recrystallized from ethyl acetate-alcohol-ether, to yield 46% of pure product, m.p. 126–128°.

From the reduction of the 4-methoxydiamylamino ketone hydrochloride, there was obtained the amino alcohol hydrochloride, m.p. 114.6–115.6° in a yield of 69% of crude and 53% of pure material.

When the 4-methoxydibutyl- and diamyl-amino ketones, as the free bases, were hydrogenated over Adams' catalyst, the only products isolated were dialkylamine and 4-methoxy-1-propionaphthone.

When the 4-chloro-di-*n*-butylamino ketone was hydrogenated and the catalyst removed by filtration, gravimetric determination of chloride on an aliquot portion indicated 71% hydrogenolysis of the ring chlorine. No pure product could be isolated.

The hydrogenation of 14.0 g. (0.0756 mole) of α,α-dimethyl-β-di-*n*-propylaminopropionaldehyde, prepared as described elsewhere (2) was carried out in ethyl alcohol. After removal of solvent, the residue was distilled at 20 mm. through a 4-inch Vigreux column. The following cuts were taken: (a) 0.4 g., b.p. 114–118°, n_D^{20} 1.4434; (b) 5.7 g., b.p. 118.0–119.5°, n_D^{20} 1.4449; (c) 6.8 g., b.p. 119.5–119.5°, n_D^{20} 1.4449; (d) still bottoms and hold-up, wt. 0.6 g. Fractions (b) and (c) make a combined yield of 88%.

Anal. Calc'd for $C_{11}H_{25}NO$: C, 70.53; H, 13.45.
Found: C, 70.60; H, 13.56.

Hydrogenation of amino ketones over Raney nickel. These experiments were performed with 4-methoxy-1-(β-dibutylaminopropio)naphthone. The hydrogenations were carried out in a Parr hydrogenator at 3 to 4 atmospheres. When the hydrochloride of the amino ketone was used, there was obtained 97% of di-*n*-butylammonium chloride and 97% of 4-methoxy-1-propionaphthone. When the hydrogenation was performed on the free base, there was obtained 78% of di-*n*-butylammonium chloride and 97% of 4-methoxy-1-propionaphthone.

Hydrogenation of amino ketone over palladium-charcoal. Hydrogenation of the 4-methoxy-di-*n*-butylamino ketone hydrochloride at atmospheric pressure with 10% palladium-charcoal catalyst was incomplete even after 6.5 days. There were isolated 66% of unreacted starting material, 13% of di-*n*-butylammonium chloride, and 17% of 4-methoxy-1-propionaphthone.

Reduction with aluminum amalgam. The 4-methoxy-di-*n*-butylamino ketone was reduced in the usual way (12) in moist ether. After 27 hours the ether layer was separated and the solids extracted with ether for 15 hours. The combined ether solutions were dried, concentrated, and cooled. There was obtained 14% of a white crystalline product *A*, m.p. 171.1–172.5°. Evaporation of the ether left an oil which yielded 84% of a hydrochloride *B*, m.p. 231.4–232.4°.

Anal. *A* Calc'd for $C_{44}H_{64}N_2O_4$: C, 77.15; H, 9.42.
Found: C, 76.99; H, 9.37.
B Calc'd for $C_{44}H_{66}Cl_2N_2O_4$: C, 69.72; H, 8.78.
Found: C, 69.66; H, 8.81.

The molecular weight of *A* by the micro-Rast method (20) was 695, 575, 648, theoretical for $C_{44}H_{64}N_2O_4$ being 685.

Addition of ethereal hydrogen chloride to a benzene solution of *A* yielded the dihydrochloride, m.p., after crystallization from alcohol-ether, 231.9–232.4°, mixed m.p. with *B* 227.5–228.0°.

Reductions with sodium amalgam. These were carried out with the 4-methoxydiethyl- and di-*n*-butylamino ketone hydrochlorides according to the method of Cromwell (21). The mixtures were worked up in the usual way but only oils were obtained.

Reduction with isobutylmagnesium bromide. The 4-methoxy-di-*n*-butylamino ketone as an ether solution was added to the isobutyl Grignard reagent. About 34% of what appeared to be isobutane was collected in a dry ice trap. From a concentrated sulfuric acid trap there was obtained a small amount of hydrocarbon.

The Grignard reaction mixture was treated in the usual way to yield a basic product. However, neither this basic material nor its hydrochloride could be crystallized.

Reductions with aluminum isopropoxide. The reduction of the 4-chlorodiethylamino ketone hydriodide is typical. It was carried out under nitrogen in an all-glass apparatus (1). After an hour 95% of the theoretical amount of acetone was obtained. The mixture was poured on an excess of iced sodium hydroxide solution and steam distilled at reduced pressure until there was no longer a detectable odor of diethylamine. The residual oil was converted to the hydrochloride, m.p. 109–111° after recrystallization from acetone-ether and 112–114° after further recrystallization from ethyl acetate; yield 5%.

Another reduction was carried out with the diethylamino ketone hydriodide at 250 mm. pressure. After eight hours, 72% of the theoretical amount of acetone was obtained. The mixture was worked up as before and the yield of amino alcohol, m.p. 110–111°, was 8%.

Several other similar experiments were carried out. Four reductions of the diethylamino ketone hydrochloride were run at atmospheric pressure. The yield in each case was 0% except one in which a 2% yield of amino alcohol was obtained. When the reduction was repeated but at 250 mm. pressure, the yield of crude amino alcohol was 5%. Where the reduction was run with the free base, no amino alcohol was obtained.

When the 4-methoxydiethylamino ketone hydrochloride was reduced, 56% of the theoretical amount of acetone was obtained in 13 hours. The reaction mixture was treated in the usual way but the basic fraction, isolated as a black oily hydrochloride, gave no crystalline material. A neutral, amorphous apparently polymeric material, which accounted for about 87% of the starting amino ketone, was also isolated.

SUMMARY

A number of Mannich bases have been prepared from 4-methoxy- and 4-chloro-1-acetonaphthone. These Mannich bases have been reduced to α-(2-dialkylaminoethyl)-4-chloro- and -4-methoxy-1-naphthalenemethanols.

An interesting structural limitation of the Mannich reaction is the failure of the branched chain ketones 4-methoxy-1-isobutyronaphthone and isobutyrophenone to give a Mannich base even under vigorous conditions. Diisopropyl ketone seems to represent a borderline case.

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