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ATTEMPTS TO FIND NEW ANTIMALARIALS. PHENANTHRYL- AND QUINOLYL-ALKAMINES OF THE TYPE $RCHOH(CH_2)_{3\text{-}11}N(C_4H_9)_2$

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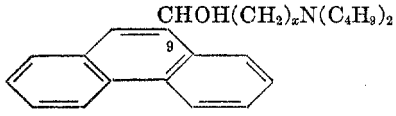
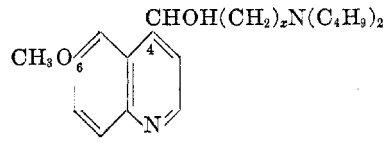
The results of screening a large number of compounds for antimalarial activity (1) indicated that compounds of the type $RCHOH(CH_2)_xNR'_2$ often showed strong antimalarial action, especially if R was 9-phenanthryl- or 6-methoxy-4-quinolyl- and x was 1 or 2. This paper reports the synthesis of two series of amino alcohols belonging to this class. In the phenanthrene series (I) x varies from 3 to 11; in the quinoline series (II) x is 3 or 6–11. The choice of the *n*-butyl group in both series was dictated by the fact that in any series of amino alcohols in which activity was found the dibutylamino homolog consistently showed some activity. In this way we hoped to get an indication of any potentially useful subgroup of types I and II without making an inordinately large number of compounds.



I



II

Our basic process for preparing I and II involved the reaction of the appropriate aromatic aldehyde with ω-dibutylaminoalkylmagnesium chlorides, and was derived from Marxer's excellent paper (2) describing compounds of the general formula $R_2N(CH_2)_3MgX$. We found that by this procedure the higher homologs $(C_4H_9)_2N(CH_2)_{6\text{-}11}MgCl$, could also be obtained without difficulty. Although Marxer (2) described the preparation of 5-diethylaminopentylmagnesium chloride (in unsatisfactory yield), we could convert neither 5-dibutylaminopentyl chloride nor 4-dibutylaminobutyl chloride to its corresponding Grignard reagent, probably due to the ready cyclization of the halides to the piperidinium and pyrrolidinium derivatives respectively.

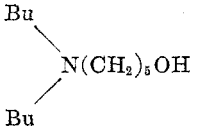
Addition of these Grignard reagents to 9-phenanthrenecarboxaldehyde and 6-methoxy-4-quinolinecarboxaldehyde proceeded in a normal manner to give modest yields of the expected secondary alcohols. Reduction by the Grignard reagent was also a significant side reaction and 9-phenanthrenemethanol and 6-methoxy-4-quinolinemethanol were usually formed in appreciable quantity. The use of the organolithium analog in place of the Grignard reagent did not prevent this undesired side reaction.

We were unable to prepare amino alcohols of type I where x = 4 and 5 by the above-outlined reaction sequence due to the inaccessibility, as stated before, of the necessary Grignard reagents. The synthesis of these homologs (as well as an alternate synthesis of the one in which x = 3) was achieved from 9-phenanthrylmagnesium bromide and the appropriate amino aldehydes or analogous amino

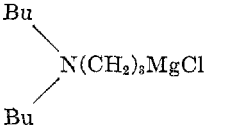
nitriles with subsequent catalytic reduction of the resulting amino ketones. Inasmuch as organometallic compounds involving the 4-position of quinoline are unknown, we did not attempt the synthesis of type II by this latter approach.

The sequence of reactions usually used in the synthesis of the requisite Grignard reagents was as follows: α,ω-glycol → chlorohydrin → ω-dibutylamino alcohol → halide → Grignard reagent. The commercially available trimethylene chlorobromide and undecylenyl alcohol were starting points for the first and last members of the series, respectively. Since at the time this work was done tetramethylene and pentamethylene glycols were not available at a reasonable cost alternative approaches to the corresponding amino alcohols were investigated.

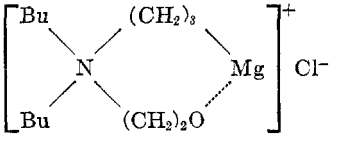
Of the several procedures tried for the preparation of 5-dibutylamino-1-pentanol (III), best results were achieved in the catalytic debenzylation of 1-benzyloxy-5-dibutylaminopentane hydrochloride.[1] It is noteworthy that an obvious possible route to III, namely, the reaction of 3-dibutylaminopropylmagnesium chloride (IV) with ethylene oxide, produced instead 2-dibutylaminoethanol. The reaction may proceed through the cyclic intermediate (V) with the elimination of propene.



III



IV



V

The best approach found for the synthesis of ω-dibutylaminobutyraldehyde (for I, x = 3) involved the reaction of IV with ethyl orthoformate (4) which yielded the diethyl acetal of ω-dibutylaminobutyraldehyde in about 60% yield. Mild acid hydrolysis afforded the free aldehyde in 86% yield. It is remarkably stable and can be distilled at atmospheric pressure. δ-Dibutylaminovaleraldehyde could be obtained in low yield by the reaction of IV with allyl bromide and ozonization of the resultant 6-dibutylamino-1-hexene in hydrochloric acid. ω-Dibutylaminocaproaldehyde was prepared from 4-penten-1-ol. The latter was converted to the Grignard reagent (*via* the chloride) which with ethylene oxide gave 6-hepten-1-ol. Chlorination of this alcohol (thionyl chloride), reaction of the chloride with dibutylamine, and ozonization of the thus-formed 7-dibutylamino-1-heptene gave the desired aldehyde.

In attempts to prepare compounds analogous to I and II in the fluorene and indole series, 9-fluorenecarboxaldehyde or 1-methyl-3-indolecarboxaldehyde (5) and IV gave unpromising reaction mixtures. Xanthone gave the unsaturated 9-(3-dibutylaminopropylidene)xanthene rather than the expected tertiary alcohol, while 1,2,3,4-tetrahydro-9-phenanthrenecarboxaldehyde and 9-acetyl-1,2,3,4-tetrahydrophenanthrene reacted with IV in the normal manner to give

[1] This compound was prepared by reaction of 3-benzyloxypropylmagnesium chloride (3) with ethylene oxide and subsequent reaction of the product with thionyl chloride, then dibutylamine.

respectively, 4-dibutylamino-1-(1,2,3,4-tetrahydro-9-phenanthryl)-1-butanol and 5-dibutylamino-2-(1,2,3,4-tetrahydro-9-phenanthryl)-2-pentanol.

Type I amino alcohols form stable salts which are, in general, insoluble or sparingly soluble in water. As the chain length increases the hydrochlorides tend to become soluble in ether and benzene. The lactates are much more soluble in water, and some are good emulsifying agents. These characteristics also apply generally to the intermediate aliphatic amino alcohols. Type II amino alcohols, on the other hand, do form water-soluble salts. It was difficult or impossible to obtain crystalline the hydrochlorides of these amino alcohols.

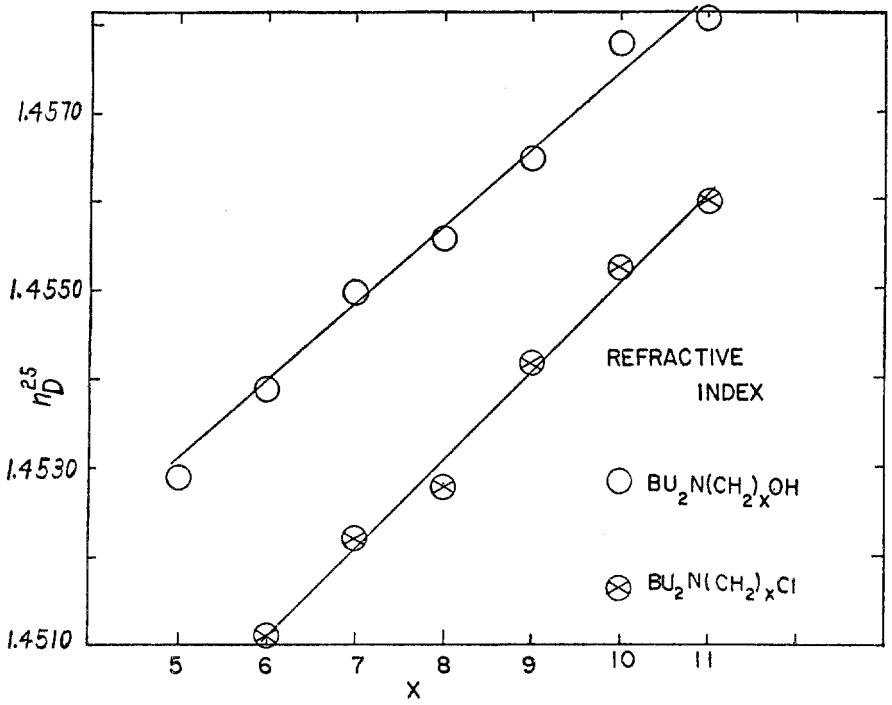


FIG. 1. PLOT OF REFRACTIVE INDEX *versus* CHAIN LENGTH FOR ω-DIBUTYLAMINO ALCOHOLS AND CHLORIDES.

None of the amino alcohols of type I and II showed noteworthy activity in blood-induced *gallinaceum* malaria in chicks. The first members of the series (x = 3) were fairly effective at the maximum tolerated dose (1).

EXPERIMENTAL[2, 3]

INTERMEDIATES

Hexamethylene chlorohydrin was prepared by the method of Coleman and Bywater (6); *cf.* (7).

[2] This work was completed in 1945 before the availability of lithium aluminum hydride, a reagent which in all probability, would have facilitated some of the preparations.

[3] Melting points are uncorrected.

Heptamethylene chlorohydrin (8) was prepared in 71% yield by the same general method; b.p. 122–124°/12 mm., m.p. 5°, n_D^{25} 1.4559.

Octamethylene chlorohydrin (8) was prepared as above in 85% yield; b.p. 130–140°/10 mm. (mainly at 134–136°), n_D^{25} 1.4572.

Nonamethylene chlorohydrin (8). Nonamethylene glycol (92 g.), 655 ml. of conc'd HCl, and 205 ml. of water were heated on the steam-bath for 24 hours while being continuously extracted with petroleum ether (b.p. 100–140°) (since this glycol and higher homologs are noticeably soluble in toluene) (8); yield 97 g. (96%), b.p. 100°/0.25 mm., m.p. 24°.

Decamethylene chlorohydrin (8) was prepared as above, using 9 *N* hydrochloric acid, in 90% yield; b.p. 110°/0.5 mm.

Undecamethylene bromohydrin. Undecylenyl alcohol (Givaudan-Delawanna, Inc., New York, N. Y.; this material was redistilled, b.p. 132–134°/11 mm., m.p. of the phenylurethan 52–52.8°) was refluxed for five hours with excess acetic anhydride. The resultant *11-undecylenyl acetate* (100 g., b.p. 145–147°/14.5 mm.) in 2 l. of benzene containing 5 g. of benzoyl peroxide was saturated by a rapid stream of hydrogen bromide while the temperature was kept below 15°. The yield of *11-bromoundecyl acetate* (9) was 103 g. (74%); b.p. 140–143°/1 mm., m.p. 13–14.5°, n_D^{25} 1.4620. Hydrolysis with ethanol and *p*-toluenesulfonic acid gave the desired bromohydrin, m.p. 44–46°.

Anal. Calc'd for $C_{11}H_{23}BrO$: M.W. 251.21: C, 52.58; H, 9.23.
Found: C, 53.14; H, 9.44.

The *phenylurethan* had the m.p. 69–72°.

Anal. Calc'd for $C_{18}H_{28}BrNO_2$, M.W. 370.33: C, 58.38; H, 7.62.
Found: C, 58.40; H, 7.76.

Oxidation of the bromohydrin (CrO_3, glacial acetic acid), gave 11-bromoundecylic acid (10), m.p. 46–47.5° alone or in mixture with an authentic specimen.

5-Dibutylamino-1-pentanol. To 30.5 g. of 5-dibutylaminopentylbenzyl ether in 250 ml.of absolute ethanol was added 3.7 g. of anhydrous HCl, then 15 g. of 5% palladium-charcoal. The mixture absorbed 2500 ml. of hydrogen (26°, 750 mm.). The product had the b.p. 95°/0.15 mm., n_D^{26} 1.4523.

Anal. Calc'd for $C_{13}H_{29}NO$, M.W. 215.37: C, 72.49; H, 13.57.
Found: C, 72.45; H, 13.34.

6-Dibutylamino-1-hexanol. Refluxing 50 g. of hexamethylene chlorohydrin with 150 g. of dibutylamine for 16 hours gave a good yield of 6-dibutylamino-1-hexanol, b.p. 121°/1 mm., n_D^{24} 1.4534.

Anal. Calc'd for $C_{14}H_{31}NO$, M.W. 229.4: C, 73.30; H, 13.62.
Found: C, 73.33; H, 13.64.

7-Dibutylamino-1-heptanol. This compound was prepared as described above in 95% yield (reflux time 30 hours); b.p. 110°/0.1 mm., n_D^{25} 1.4450.

Anal. Calc'd for $C_{15}H_{33}NO$, M.W. 243.42: C, 74.01; H, 13.67.
Found: C, 73.58; H, 13.38.

8-Dibutylamino-1-octanol. The reflux time was 30 hours; yield 91%, b.p. 138–145°/1 mm., n_D^{24} 1.4560.

Anal. Calc'd for $C_{16}H_{35}NO$, M.W. 257.45: C, 74.64; H, 13.70.
Found: C, 73.85; H, 13.46.

9-Dibutylamino-1-nonanol. The yield was 80% after refluxing for 16 hours; b.p. 132°/0.2 mm., n_D^{24} 1.4569.

Anal. Calc'd for $C_{17}H_{37}NO$, M.W. 271.48: C, 75.24; H, 13.74.
Found: C, 75.80; H, 13.54.

10-Dibutylamino-1-decanol. The yield was 89% after a reflux time of 24 hours; b.p. 135°/0.25 mm., n_D^{25} 1.4580.

Anal. Calc'd for $C_{18}H_{39}NO$, M.W. 285.50: C, 75.72; H, 13.77.
Found: C, 75.68; H, 13.72.

11-Dibutylamino-1-undecanol. Refluxing 100 g. of undecamethylene bromohydrin and 312 g. of dibutylamine for 5.5 hours gave this alcohol in a yield of 81%, b.p. 142–152°/0.1 mm., n_D^{27} 1.4573.

Anal. Calc'd for $C_{19}H_{41}NO$, M.W. 299.5: C, 76.18; H, 13.55.
Found: C, 76.42; H, 14.00.

3-Dibutylamino-1-chloropropane was prepared as described by Marxer (2).

5-Dibutylamino-1-chloropentane. By the action of dibutylamine on pentamethylene chlorobromide (11) or thionyl chloride on 5-dibutylamino-1-pentanol, an ether-soluble substance (presumably 5-dibutylamino-1-chloropentane) was obtained which was fairly stable in the cold but which, on attempted distillation, gave *1-butylpiperidine hydrochloride*, m.p. 236–238° (12).

Anal. Calc'd for $C_9H_{20}ClN$, M.W. 177.72: C, 61.0; H, 11.4.
Found: C, 61.04; H, 11.48.

6-Dibutylamino-1-chlorohexane. To 22.9 g. of 6-dibutylamino-1-hexanol in 80 ml. of dry, alcohol-free chloroform was added at *ca.* 5° 10 ml. of thionyl chloride. After refluxing for one hour the mixture was washed with water (the chloride hydrochloride remaining in the chloroform layer), then aqueous alkali, and the chloroform evaporated *in vacuo*. The residue was dissolved in ether, clarified with Norit, and the basic material extracted with hydrochloric acid. The base was liberated with alkali and dried over calcium sulfate; b.p. 95°/0.1 mm., n_D^{25} 1.4511.

Anal. Calc'd for $C_{14}H_{30}ClN$, M.W. 247.85: C, 67.84; H, 12.20.
Found: C, 68.08; H, 11.70.

7-Dibutylamino-1-chloroheptane. The yield was 78%; b.p. 115°/1 mm., n_D^{28} 1.4510.

Anal. Calc'd for $C_{15}H_{32}ClN$, M.W. 261.88: C, 68.79; H, 12.32.
Found: C, 69.02; H, 12.27.

8-Dibutylamino-1-chlorooctane. The yield was 87%; b.p. 116°/0.3 mm., n_D^{23} 1.4340.

Anal. Calc'd for $C_{16}H_{34}ClN$, M.W. 275.90: C, 69.65; H, 12.42.
Found: C, 69.82; H, 12.86.

9-Dibutylamino-1-chlorononane; yield 72%, b.p. 128°/0.5 mm., $n_D^{26.5}$ 1.4537.

Anal. Calc'd for $C_{17}H_{36}ClN$, M.W. 289.93: C, 70.43; H, 12.52.
Found: C, 70.91; H, 12.80.

10-Dibutylamino-1-chlorodecane; yield 92%, b.p. 133°/0.5 mm., n_D^{25} 1.4553, d_4^{25} 0.85.

Anal. Calc'd for $C_{18}H_{38}ClN$, M.W. 303.95: C, 71.12; H, 12.60.
Found: C, 71.73; H, 12.37.

11-Dibutylamino-1-chloroundecane; yield 90%, b.p. 145°/0.5 mm., n_D^{26} 1.4557.

Anal. Calc'd for $C_{19}H_{40}ClN$, M.W. 317.98: C, 71.76; H, 12.68.
Found: C, 71.14; H, 12.14.

As is evident from Figure 1, there is a linear relationship between refractive index and length of alkyl chain for the ω-dibutylamino alcohols, as well as for the ω-dibutylamino chlorides.

Grignard reagents from dibutylamino halides. By observing certain precautions, the above halides may easily be converted to Grignard reagents. The chief factors affecting the conversion can be enumerated as follows:

1. Moisture must be rigorously excluded. We used an apparatus in which ether from ethereal methylmagnesium iodide was directly distilled into the reaction flask. This ether was used both to help in drying the apparatus, and as a reaction solvent.

2. The magnesium should be activated with methyl iodide or ethyl bromide. We used a reaction flask with a stopcock sealed to the bottom for removing the activating solution prior to the introduction of the amino chloride.

3. The minimal amount of ether should be used in the initial phase of the reaction.

4. Stirring should be employed sparingly, if at all, until the reaction is well under way.

5. Once started, the reaction should be continued unabated until complete.

After activating the magnesium (a large excess is advantageous) with about 5 ml. of methyl iodide, employing vigorous stirring, and removal of the activating solution, a small amount of ether was distilled into the reaction flask and about 5 ml. of the amino halide added. The reaction usually started promptly, warming being rarely necessary. The reaction was kept going steadily by the addition of the amino chloride, diluted if desired

with one or two volumes of ordinary anhydrous ether. The desired concentration was maintained in the reaction flask by distilling in ether from the methylmagnesium iodide flask. Moderate stirring was usually employed. The reaction was completed by heating at reflux for 0.5 hour. The yields were usually 80–85%.

These Grignard reagents are fairly insoluble in ether, and crystallize either at once, or on long standing. They are easily soluble in benzene. A normal color test (Gilman's color test I) is obtained with Michler's ketone and iodine in acetic acid. We were unable to prepare the Grignard reagents in which the halogen and nitrogen atoms were separated by 4 and 5 carbon atoms respectively.

γ-Dibutylaminobutyraldehyde.[4] Ethyl orthoformate (100 g.) and 320 ml. of 0.85 *N* 3-dibutylaminopropylmagnesium chloride (IV) in benzene were kept at 65° for 15 hours to give 47 g. (60%) of *γ-dibutylaminobutyraldehyde diethylacetal*, b.p. 90–110°/2 mm., and on redistillation, b.p. 149.5°/9 mm., n_D^{29} 1.4330.

Anal. Calc'd for $C_{16}H_{35}NO_2$, M.W. 273.45: C, 70.27; H, 12.90.
Found: C, 68.97; H, 13.17.

On mild acid hydrolysis this gave the aldehyde (86% yield) of b.p. 235°; 71.0°/0.08 mm. n_D^{30} 1.4398 (1.4460 after 16 hours).

Anal. Calc'd for $C_{12}H_{25}NO$, M.W. 199.33: C, 72.30; H, 12.64.
Found: C, 72.34; H, 12.60.

The *2,4-dinitrophenylhydrazone* melted at 65–67°.

Anal. Calc'd for $C_{18}H_{29}N_5O_4$, M.W. 379.45: C, 56.97; H, 7.70.
Found: C, 56.77; H, 7.65.

6-Dibutylamino-1-hexene. Allyl bromide (22 g.) and 275 ml. of 0.62 *N* IV in benzene were mixed at 35° and left overnight. The resultant product, after two distillations had b.p. 63–64°/0.5 mm., n_D^{26} 1.4410.

Anal. Calc'd for $C_{14}H_{29}N$, M.W. 211.38: C, 79.54; H, 13.83.
Found: C, 76.45; H, 13.64.

Catalytic hydrogenation indicated one ethylenic linkage in the molecule.

δ-Dibutylaminovaleraldehyde.[5] The above olefin (10 g.), 100 ml. of water, and the theoretical amount of 2.5 *N* HCl were ozonized with 2.5% ozone at the rate of 10 l. per hour. The solution was poured into excess K_2CO_3 solution at below 0° and quickly extracted with petroleum ether, (b.p. 85–100°). After drying with $CaSO_4$ the crude aldehyde was used directly in the Grignard reaction. It boiled at 89°/0.5 mm. The *2,4-dinitrophenylhydrazone* melted at 58.5–62°.

Anal. Calc'd for $C_{19}H_{31}N_5O_4$, M.W. 393.48: C, 57.99; H, 7.94.
Found: C, 57.70; H, 7.63.

The *acetal* was prepared by reaction of the aldehyde with alcoholic hydrogen chloride at 5° for 48 hours; b.p. 154–155°/8.5 mm., $n_D^{25.5}$ 1.4371, n_D^{30} 1.4355.

Anal. Calc'd for $C_{17}H_{37}NO_2$, M.W. 287.48: C, 71.02; H, 12.97.
Found: C, 71.12; H, 12.22.

7-Chloro-1-heptene. 5-Chloro-1-pentene, b.p. 102–104°, n_D^{20} 1.4303, was prepared in 65% yield from 4-penten-1-ol (11) with thionyl chloride and pyridine in bromobenzene. The Grignard reagent of this chloride and ethylene oxide gave 6-hepten-1-ol, b.p. 88°/20 mm., n_D^{20} 1.4440; lit. (14) b.p. 105°/20 mm., n_D^{20} 1.4403. The alcohol (10.6 g.) was chlorinated with 7.3 ml. of thionyl chloride, 8.1 ml. of pyridine, and 300 ml. of dry chloroform. The product had b.p. 79–80°/41 mm., n_D^{25} 1.4396; yield 65%.

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[4] The Stephen reaction (13) on ω-dibutylaminobutyronitrile gave none of this aldehyde; ω-chlorobutyronitrile (6.6 g.), 17 g. of anhydrous $SnCl_2$, and 80 ml. of dry ether gave, after 18 hours at 0°, a 10% yield of *ω-chlorobutyraldehyde* as the *2,4-dinitrophenylhydrazone*, m.p. 132° (from alcohol). *Anal.* Calc'd for $C_{10}H_{11}ClN_4O_4$: C, 41.89; H, 3.87. Found: C, 41.23; H, 4.05.

[5] Attempts to prepare this aldehyde by Rosenmund reduction of the corresponding acid chloride failed.

Anal. Calc'd for $C_7H_{13}Cl$, M.W. 132.63: C, 63.39; H, 9.88.
Found: C, 62.67; H, 9.60.

5-Iodo-1-pentene. The reaction of 5-chloro-1-pentene with sodium iodide in acetone gave the iodo compound, b.p. 150°, n_D^{25} 1.5162.

Anal. Calc'd for C_5H_9I, M.W. 196.04: C, 30.63; H, 4.63.
Found: C, 31.00; H, 4.56.

7-Dibutylamino-1-heptene. The above chloride (6.7 g.) and 13.1 g. of dibutylamine, kept at 180° for 6 hours gave 8.5 ml. of product, b.p. 92–94°/0.4 mm., 78°/0.2 mm., n_D^{25} 1.4427.

Anal. Calc'd for $C_{15}H_{31}N$, M.W. 225.41: C, 79.92; H, 13.87.
Found: C, 80.07; H, 13.68.

The *chloroplatinate* had the m.p. 169–171°.

Anal. Calc'd for $C_{30}H_{64}Cl_6N_2Pt$, M.W. 860.81: C, 41.86; H, 7.49; Pt, 22.68.
Found: C, 41.72; H, 6.50; Pt, 22.89.

ε-Dibutylaminocaproaldehyde. Ozonization of 10 g. of 7-dibutylamino-1-heptene as described for 6-dibutylamino-1-hexene gave the desired amino aldehyde which was used in the crude state for the reaction with 9-phenanthrylmagnesium bromide. The *2,4-dinitrophenylhydrazone* was recrystallized from ethanol; m.p. 63–64°.

Anal. Calc'd for $C_{20}H_{33}N_5O_4$, M.W. 407.50: C, 58.95; H, 8.16.
Found: C, 59.12; H, 8.70.

γ-Dibutylaminobutyronitrile. 3-Dibutylaminopropyl chloride (39.9 g.), 14 g. of 95% potassium cyanide, 0.2 g. of copper sulfate, 2.0 g. of sodium iodide, and 200 ml. of 90% alcohol, refluxed 5 hours gave 79.5% of the nitrile, b.p. 142°/10 mm., n_D^{25} 1.4411. The *picrate* (from ethyl acetate-ether) melted at 95–97°.

Anal. Calc'd for $C_{18}H_{27}N_5O_7$, M.W. 425.44: C, 50.81; H, 6.40.
Found: C, 50.69; H, 6.32.

This compound was also prepared in 85% yield from dibutylamine and γ-chlorobutyronitrile.

ε-Dibutylaminocapronitrile. Excess dibutylamine and ε-chlorocapronitrile (11) heated at 130°, gave the amino nitrile, b.p. 109–111°/1 mm. The *aurichloride,* from aqueous alcohol, melted at 95–97°.

Anal. Calc'd for $C_{14}H_{29}AuCl_4N_2$, M.W. 564.42: C, 29.79; H, 5.18; Au, 34.94.
Found: C, 29.46; H, 5.26; Au, 35.19.

PHENANTHRYL AMINO ALCOHOLS

These amino alcohols were difficult to purify and characterize. Their salts could rarely be obtained crystalline and the bases were high-boiling viscous oils. Molecular distillation of the latter at 10^{-5} to 10^{-6} mm. appeared to be the best method of purification. To determine whether dehydration of the secondary alcohols had taken place during their preparation and purification, the final products were subjected to catalytic hydrogenation. In no instance was absorption of hydrogen observed.

4-Dibutylamino-1-(9-phenanthryl)-1-butanol hydrochloride. (*a*) *From dibutylaminopropyl chloride.* The Grignard reagent from 15 g. of 3-dibutylamino-1-chloropropane was added to 7.1 g. of 9-phenanthrenecarboxaldehyde in benzene. After 5 hours at 45–50° the product was isolated as the hydrochloride which crystallized from ethanol; m.p. 145–147°.

Anal. Calc'd for $C_{26}H_{36}ClNO$, M.W. 414.01: C, 75.42; H, 8.76.
Found: C, 74.84; H, 9.06.

(*b*) *From γ-dibutylaminobutyronitrile.* γ-Dibutylaminobutyronitrile (24.5 g.) was added to 0.1 mole of ethereal 9-phenanthrylmagnesium bromide.[6] After refluxing for 15 hours the mixture gave 33.6 g. of brown oil which was converted to the oily sulfate, insoluble in water and ether. It was converted to the *hydrochloride* of *4-dibutylamino-1-(9-phenanthryl)-1-butanone,* m.p. 121–122° (from alcohol). An air-dried sample was analyzed.

Anal. Calc'd for $C_{26}H_{34}ClNO \cdot H_2O$, M.W. 430.02: C, 72.62; H, 8.44.
Found: C, 73.06; H, 8.17.

[6] This Grignard reagent shows the interesting property of chemiluminescence when its ethereal solution is poured in air.

Hydrogenation of this amino ketone (methanol, platinum oxide) gave the corresponding alcohol described in (*a*). This alcohol was also prepared from 9-phenanthrylmagnesium bromide and ω-dibutylaminobutyraldehyde.

5-Dibutylamino-1-(9-phenanthryl)-1-pentanol. The Grignard reagent from 20 g. of 9-bromophenanthrene and the crude δ-dibutylaminovaleraldehyde obtained by ozonizing 6.4 g. of 6-dibutylamino-1-hexene gave 6 g. of oily hydrochloride. Distillation of the base at 185° (10^{-6} mm.) gave a thick oil.

Anal. Calc'd for $C_{27}H_{37}NO$, M.W. 391.58: C, 82.81; H, 9.53.
Found: C, 82.12; H, 9.72.

6-Dibutylamino-1-(9-phenanthryl)-1-hexanol hydrochloride. Addition of 9.5 g. of ε-dibutylaminocapronitrile to the phenanthrylmagnesium bromide from 11.3 g. of 9-bromophenanthrene gave *6-dibutylamino-1-(9-phenanthryl)-1-hexanone*, whose *hydrochloride* had m.p. 120–121° (from acetone).

Anal. Calc'd for $C_{25}H_{38}ClNO$, M.W. 440.14: C, 76.40; H, 8.70.
Found: C, 75.99; H, 8.54.

This hydrochloride, alcohol, and platinum oxide absorbed hydrogen gradually to the corresponding hexanol hydrochloride which crystallized after 8 months; m.p. 132–135° (sinters at 105°).

Anal. Calc'd for $C_{28}H_{40}ClNO$, M.W. 442.07: C, 76.07; H, 9.12.
Found: C, 75.55; H 9.17.

This amino alcohol hydrochloride could also be prepared from 9-phenanthrylmagnesium bromide and δ-dibutylaminocaproaldehyde. Chromic acid oxidation of the alcohol thus obtained in acetic acid and benzene gave 6-dibutylamino-1-(9-phenanthryl)-1-hexanone whose hydrochloride was identical with that described above.

7-Dibutylamino-1-(9-phenanthryl)-1-heptanol. The Grignard reagent from 10.4 g. of 6-dibutylamino-1-chlorohexane added to 9 g. of 9-phenanthrenecarboxaldehyde gave this product which was isolated as the oily hydrochloride. The liberated base was distilled at 10^{-5} mm.

Anal. Calc'd for $C_{29}H_{41}NO$, M.W. 419.63: C, 83.00; H, 9.85.
Found: C, 82.77; H, 9.45.

8-Dibutylamino-1-(9-phenanthryl)-1-octanol. The addition of 230 ml. of 0.4 *N* 7-dibutylamino-1-heptylmagnesium chloride to 0.1 mole of 9-phenanthrenecarboxaldehyde gave 5 g. of 9-phenanthrenemethanol, m.p. 149–151.5° and 7.8 g. of amino alcohol after a distillation at 180° (10^{-6} mm.).

Anal. Calc'd for $C_{30}H_{43}NO$, M.W. 433.65: C, 83.07; H, 9.99.
Found: C, 82.95; H, 10.33.

In an experiment using 7-dibutylamino-1-heptyllithium (from 3.4 g. of powdered lithium, 52 g. of 7-dibutylamino-1-chloroheptane, and 75 ml. of petroleum ether, b.p. 30–60°) the yield of 9-phenanthrenemethanol was not decreased.

9-Dibutylamino-1-(9-phenanthryl)-1-nonanol. To 0.1 mole of 8-dibutylaminoöctylmagnesium chloride in benzene-petroleum ether (b.p. 30–60°) cooled to −70° was added 0.1 mole of ethereal 9-phenanthrenecarboxaldehyde to give, after distillation of the 25.5 g. of crude base at 200° (10^{-5} mm.), 10.2 g. of product.

Anal. Calc'd for $C_{31}H_{45}NO$, M.W. 447.7: C, 83.16; H, 10.13.
Found: C, 83.12; H, 10.21.

10-Dibutylamino-1-(9-phenanthryl)-1-decanol. This compound was prepared as described for the nonanol homolog except that toluene was used as a solvent for the aldehyde and the order of addition was reversed.

Anal. Calc'd for $C_{32}H_{47}NO$, M.W. 461.71: C, 83.24; H, 10.26.
Found: C, 82.42; H, 10.37.

11-Dibutylamino-1-(9-phenanthryl)-1-undecanol. The addition of 250 ml. of 0.6 *N* 10-dibutylaminodecylmagnesium chloride to 30.5 g. of 9-phenanthrenecarboxaldehyde at −70° and molecular distillation of the product at 200° (10^{-6} mm.) gave 22.6 g. of base.

Anal. Calc'd for $C_{33}H_{49}NO$, M.W. 475.7: C, 83.31; H, 10.38.
Found: C, 83.56; H, 10.17.

12-Dibutylamino-1-(9-phenanthryl)-1-dodecanol. This product was obtained as described for the three lower homologs. Yield, 16.7 g., distilling at 210°/10^{-5} mm.

Anal. Calc'd for $C_{34}H_{51}NO$, M.W. 489.76: C, 83.37; H, 10.50; N, 2.86.
Found: C, 83.36; H, 10.67; N, 2.86.

QUINOLYL AMINO ALCOHOLS

These amino alcohols were difficult to purify and characterize. Their salts could rarely be obtained crystalline and the bases were high-boiling viscous oils. Molecular distillation of the latter at 10^{-5} to 10^{-6} mm. appeared to be the best method of purification. To determine whether dehydration of the secondary alcohols had taken place during their preparation and purification, the final products were subjected to catalytic hydrogenation. In no instance was absorption of hydrogen observed.

4-Dibutylamino-1-(6-methoxy-4-quinolyl)-1-butanol hydrochloride. 6-Methoxy-4-quinolinecarboxaldehyde (0.1 mole) in ether was added to excess ethereal IV. After stirring overnight the basic fraction was separated with hydrochloric acid. The base was again liberated and molecularly distilled at 150–170°/10^{-5} mm.; yield 26.1 g. The dihydrochloride crystallized from ethanol-ether; m.p. 191–192°.

Anal. Calc'd for $C_{22}H_{36}Cl_2O_2 \cdot \frac{1}{4}H_2O$, M.W. 435.95: C, 60.61; H, 8.44.
Found: C, 60.36; H, 8.40.

7-Dibutylamino-1-(6-methoxy-4-quinolyl)-1-heptanol. 6-Dibutylaminohexylmagnesium chloride (from 53 g. of chloride) was brought to reaction with 22.4 g. of the aldehyde in benzene. Molecular distillation of the product at 175° (10^{-6} mm.) gave 6.3 g.

Anal. Calc'd for $C_{25}H_{40}N_2O_2$, M.W. 400.6: C, 74.95; H, 10.06.
Found: C, 74.54; H, 9.64.

8-Dibutylamino-1-(6-methoxy-4-quinolyl)-1-octanol. To 13 g. of 6-methoxy-4-quinolinecarboxaldehyde in 500 ml. of boiling toluene was added 180 ml. of 0.65 *N* 7-dibutylaminoheptylmagnesium chloride to give 5 g. of 6-methoxy-4-quinolinemethanol, 18 g. of low-boiling basic material (presumably containing dibutyl-5-hexenylamine), and 18 g. of a viscous oil distilling at 175° (10^{-5} mm.).

Anal. Calc'd for $C_{26}H_{42}N_2O_2$, M.W. 414.62; C. 75.31; H, 10.21.
Found: C, 74.44; H, 10.66.

9-Dibutylamino-1-(6-methoxy-4-quinolyl)-1-nonanol. 6-Methoxy-4-quinolinecarboxaldehyde (29 g.) in toluene was added to 0.15 mole of 8-dibutylaminoöctylmagnesium chloride cooled to −70°. Molecular distillation of the product at 190° (10^{-5} mm.) gave 7 g. of oil.

Anal. Calc'd for $C_{27}H_{44}N_2O_2$, M.W. 428.65: C, 75.65; H, 10.35.
Found: C, 74.39; H, 9.99.

10-Dibutylamino-1-(6-methoxy-4-quinolyl)-1-decanol. To 25.8 g. of 6-methoxy-4-quinolinecarboxaldehyde cooled to −70° was added 0.14 mole of 9-dibutylaminononylmagnesium chloride to give 16.5 g. of crude 6-methoxy-4-quinolinemethanol and 14.5 g. (distilled at 10^{-5} mm.) of the desired product.

Anal. Calc'd for $C_{23}H_{46}N_2O_2$, M.W. 442.67: C, 75.97; H, 10.48.
Found: C, 76.08; H, 10.38.

11-Dibutylamino-1-(6-methoxy-4-quinolyl)-1-undecanol. This compound was prepared as described for the previous one.

Anal. Calc'd for $C_{29}H_{48}N_2O_2$, M.W. 456.7: C, 76.27; H, 10.59.
Found: C, 76.70; H, 11.22.

12-Dibutylamino-1-(6-methoxy-4-quinolyl)-1-dodecanol. As described for the two previous homologs this compound was obtained in similar yield.

Anal. Calc'd for $C_{30}H_{50}N_2O_2$, M.W. 470.72: C, 76.54; H, 10.71.
Found: C, 76.94; H, 11.16.

MISCELLANEOUS REACTIONS

4-Dibutylamino-1-phenyl-1-butanol. Marxer (2) reports the preparation of $C_6H_5CH(OH)(CH_2)_3NBu_2$, and states that the difficultly soluble hydrochloride separates when an ethereal solution of the base is treated with 2 *N* hydrochloric acid.

On repeating this preparation, we found the hydrochloride to be readily soluble when prepared as described by Marxer, and could not effect precipitation by varying the HCl concentration. The crystalline salt, obtained by the slow evaporation of the aqueous solution, was also very soluble in water and 2 *N* HCl.

Oxidation of the carbinol with CrO_3 in glacial acetic acid led to *γ-dibutylaminobutyrophenone*, whose *semicarbazone hydrochloride* crystallized from alcohol-ether, and deliquesced in the air to a *hydrate* of m.p. 177–178°, which was not obtained anhydrous when dried over magnesium perchlorate at 30°. The *semicarbazone picrate* melted at 175–177° (from alcohol).

Anal. Calc'd for $C_{25}H_{35}N_7O_8$, M.W. 561.59: C, 53.2; H, 6.28.
Found: C, 52.96; H, 6.53.

The reaction of IV with benzophenone led to the expected tertiary carbinol, whose hydrochloride has m.p. 161–163° which is in reasonable agreement with Marxer's m.p. of 158–159° for this compound.

3-Dibutylamino-1-(9-propylidene)xanthene hydrochloride. Addition of 28 g. of xanthone to excess ethereal IV and treatment of the reaction mixture with hydrochloric acid gave 35 g. of a crystalline hydrochloride of m.p. 204–205° (from dilute alcohol).

Anal. Calc'd for $C_{24}H_{32}ClNO$, M.W. 385.96: C, 74.67; H, 8.36.
Found: C, 74.20; H, 8.48.

Hydrogenation of this compound (platinum oxide, 95% ethanol) resulted in the absorption of the amount of hydrogen calculated for one ethylenic bond.

4-Dibutylamino-1-(1,2,3,4-tetrahydro-9-phenanthryl)-1-butanol. This compound resulted in a yield of 19 g. (molecularly distilled at 150°/10^{-5} mm.), from addition of 0.1 mole of IV to 22 g. of 1,2,3,4-tetrahydro-9-phenanthrenecarboxaldehyde.

Anal. Calc'd for $C_{26}H_{34}NO$, M.W. 381.59: C, 81.9; H, 10.3.
Found: C, 82.35; H, 10.59.

5-Dibutylamino-2-(1,2,3,4-tetrahydro-9-phenanthryl)-2-pentanol. The addition of 0.1 mole of 9-acetyl-1,2,3,4-tetrahydrophenanthrene to excess ethereal IV gave an oil, insoluble in excess hydrochloric acid. Liberation of the base gave a product distilling at 150° (10^{-5} mm.).

Anal. Calc'd for $C_{27}H_{41}NO$, M.W. 395.61: C, 81.97; H, 10.45.
Found: C, 82.76; H, 10.47.

Reaction of IV with ethylene oxide (15). The Grignard reagent from 222 g. of 3-dibutylaminopropyl chloride in 500 ml. of ether and 1000 ml. of C_6H_6 was treated at −5° with 105 g. of ethylene oxide and kept overnight at room temperature. The mixture was distilled to a vapor temperature of 65°, decomposed with aqueous NH_4Cl, and extracted with ether to give, after two distillations, 80 g. (43%) of *2-dibutylaminoethanol*, b.p. 100°/0.8 mm., n_D^{24} 1.4429. The *p-nitrobenzoate* had the m.p. 95–98° alone or in mixture with an authentic specimen.

4-Benzyloxy-1-butanol. The Grignard reagent from 1 mole of 3-benzyloxypropyl chloride (3)[7] and 45 g. of gaseous formaldehyde gave 33 ml. of this alcohol, b.p. 155–167°/12 mm., n_D^{28} 1.5130; lit. (3), b.p. 157°/12 mm., (16), b.p. 146–149°/6 mm. The *3,5-dinitrobenzoate* (from ethanol) melted at 62–64°.

Anal. Calc'd for $C_{18}H_{16}N_2O_7$, M.W. 374.34: C, 57.75; H, 4.85.
Found: C, 57.77; H, 5.02.

δ-Benzyloxyvaleraldehyde. Chlorination of 23 g. of 4-benzyloxy-1-butanol below 60° with 19 g. of thionyl chloride, and 25 g. of dimethylaniline gave 16.5 g. (64%) of the chloride, b.p. 85°/0.5 mm., $n_D^{23.4}$ 1.5100; lit. (3), b.p. 135°/12 mm., n_α^{20} 1.5083. The Grignard reagent from 16 g. of this chloride and 23 g. of ethyl orthoformate, kept for 15 hours at 60°, gave *δ-benzyloxyvaleraldehyde diethylacetal*, b.p. 133–134°/2 mm., n_D^{24} 1.4757, which was hydrolyzed to the aldehyde with *N* HCl. The *2,4-dinitrophenylhydrazone* melted at 86–87°.

Anal. Calc'd for $C_{18}H_{20}N_4O_5$, M.W. 372.37: C, 58.05; H, 5.41.
Found: C, 57.87; H, 5.62.

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[7] Dimethylaniline cannot be replaced by pyridine in the preparation of this chloride.

Attempts to debenzylate this acetal (palladium-charcoal, hydrogen, ethanol) failed.

δ-Chloropentylbenzyl ether. The reaction of 0.2 mole of 3-benzyloxypropylmagnesium chloride with 11 g. of ethylene oxide below 10° with subsequent heating for one hour at 65° gave 56% of 5-benzyloxypentanol, b.p. 115°/0.2 mm., n_D^{23} 1.5090. This alcohol (200 g.), 135 g. of thionyl chloride, 15 g. of dimethylaniline, and 200 ml. of chloroform at 55–60° gave, after two distillations, 178 g. of the ether, b.p. 85–87°/0.15 mm., n_D^{25} 1.5067.

Anal. Calc'd for $C_{12}H_{17}ClO$, M.W. 212.72: C, 67.75; H, 8.06.
Found: C, 68.26; H, 8.30.

δ-Dibutylaminopentylbenzyl ether. The above ether (170 g.) and 305 g. of dibutylamine, refluxed 28 hours, gave 218 g. of product, b.p. 136°/0.2 mm., n_D^{24} 1.4823.

Anal. Calc'd for $C_{20}H_{35}NO$, M.W. 305.49: C, 78.63; H, 11.55.
Found: C, 76.50; H, 11.33.

ε-Benzyloxycaproaldehyde diethylacetal. The Grignard reagent from 47.6 g. of 5-chloropentylbenzyl ether and 50 g. of ethyl orthoformate kept at 50° for 2 hours gave 40 g. of the acetal, b.p. 117°/0.2 mm., n_D^{25} 1.4758.

Anal. Calc'd for $C_{17}H_{28}O_3$, M.W. 280.39: C, 72.82; H, 10.06.
Found: C, 72.33; H, 10.09.

Hydrolysis of the acetal with *N* HCl gave the *aldehyde*, whose *2,4-dinitrophenylhydrazone* melted at 65–67°.

Anal. Calc'd for $C_{18}H_{22}N_4O_5$, M.W. 386.40: C, 59.06; H, 5.74.
Found: C, 59.34; H, 5.81.

ε-Hydroxycaproaldehyde. ε-Benzyloxycaproaldehyde diethylacetal (2.8 g.), 2 g. of 5% palladium-charcoal, and 25 ml. of absolute ethanol[8] absorbed the calculated amount of hydrogen during 20 minutes. The resultant volatile, mobile liquid had a pungent, peppermint-like odor and may be 2-ethoxyoxacycloheptane [a similar cyclic acetal has been reported by Helferich and Sparmberg (17)] and was readily hydrolyzed to ε-hydroxycaproaldehyde, characterized as the *2,4-dinitrophenylhydrazone*, m.p. 105–106°.

Anal. Calc'd for $C_{12}H_{16}N_4O_5$, M.W. 296.28: C, 48.75; H, 5.32.
Found: C, 48.50; H, 5.56.

2-Dibutylaminomethyltetrahydrofuran. Dibutylamine, tetrahydrofurfuryl chloride, and cyclohexanol, refluxed for several days gave this base, b.p. 135–138°/18 mm., n_D^{25} 1.4481. The *aurichloride* melted at 90.5–91°.

Anal. Calc'd for $C_{13}H_{28}AuCl_4NO$, M.W. 553.39: C, 28.21; H, 5.10; Au, 35.64.
Found: C, 28.12; H, 5.01; Au, 35.60.

Hydrogenation of this compound by the method of Keimatsu and Takamoto (18), as well as by that of Natta-Regamonte and Beate (19) did not yield any appreciable quantity of 5-dibutylamino-1-pentanol.

Ethyl δ-dibutylaminovalerate. The sodio compound of 88 g. of diethyl malonate in absolute alcohol and 103 g. of dibutylaminopropyl chloride, warmed on the steam-bath, gave 56% of *diethyl γ-dibutylaminopropylmalonate*, b.p. 130°/0.2 mm., n_D^{23} 1.4434. Refluxing this ester for 18 hours with 300 ml. of 5 *N* HCl and esterification of the resultant acid with alcoholic HCl gave the desired ester, b.p. 152–153°/15 mm., n_D^{24} 1.4388.

Anal. Calc'd for $C_{15}H_{31}NO_2$, M.W. 257.41: C, 70.00; H, 12.16.
Found: C, 69.74; H, 12.00.

The *chloroplatinate* (from aqueous alcohol) melted at 117°.

Anal. Calc'd for $C_{30}H_{64}Cl_6N_2O_4Pt$, M.W. 924.80: C, 38.95; H, 6.97; Pt, 21.15.
Found: C, 38.14; H, 6.91; Pt, 21.10

The sodium and alcohol reduction (20, 21) of this ester led to a good yield of 5-dibutylamino-1-pentanol.

Ethyl α-(3-dibutylaminopropyl)acetoacetate. Ethyl sodioacetoacetate (from 65 g. of ethyl acetoacetate, 11.5 g. of sodium, and 250 ml. of absolute ethanol) and 97.8 g. of 3-dibutylaminopropyl chloride were stirred and refluxed overnight. Distillation of the product in a

[8] This reduction went slowly in methanol and failed completely in benzene, cyclohexane, dimethylaniline, or dioxane.

high vacuum at about 50° gave a 29% yield, n_D^{23} 1.4480. Distillation at 120°/0.2 mm. gave some decomposition.

Anal. Calc'd for $C_{17}H_{33}NO_3$, M.W. 299.44: C, 68.18; H, 11.32.
Found: C, 68.90; H, 11.32.

We were not able to obtain 5-dibutylamino-1-pentanol by the high pressure catalytic hydrogenation of this compound.

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SUMMARY

The synthesis of amino alcohols of the type $RCHOH(CH_2)_{3\text{-}11}N(C_4H_9)_2$ in which R is 9-phenanthryl- (I) or 6-methoxy-4-quinolyl- (II) has been achieved from the appropriate aliphatic amino Grignard reagents, amino aldehydes, or amino nitriles. The new aliphatic amino Grignard reagents were prepared by the sequence of reactions α,ω-glycol → chloro- (or bromo)- hydrin → ω-dibutylamino alcohol → halide → Grignard reagent.

In orienting experiments with 3-dibutylaminopropylmagnesium chloride, 4-dibutylamino-1-(1,2,3,4-tetrahydro-9-phenanthryl)-1-butanol and 5-dibutylamino-2-(1,2,3,4-tetrahydro-9-phenanthryl)-2-pentanol were also synthesized.

With the exception of the first member of each series I and II and the tetrahydrophenanthrylbutanol derivative, which were effective at the maximum tolerated dose, the aromatic amino alcohols were inactive as antimalarial agents.

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