[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME]

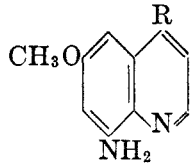
STUDIES IN THE QUINOLINE SERIES. IX. 4-SUBSTITUTED-8-AMINOQUINOLINES AND RELATED NAPHTHALENES[1]

KENNETH N. CAMPBELL, RAYMOND A. LAFORGE,[2] AND BARBARA K. CAMPBELL[3]

Received October 20, 1948

Since several of the 6-methoxy-8(alkylaminoalkylamino)lepidines prepared in connection with the antimalarial program (1, 2) have shown high antimalarial activity together with a toxicity much lower than that of the related quinolines, further work in this field seemed of interest.

As a part of this program, attempts were made to replace the 4-methyl group with other groups such as phenyl, carbethoxy, isopropyl, hydroxymethyl, and aldehyde, but considerable difficulty was experienced in obtaining the required 6-methoxy-8-amino-4-substituted quinolines, and in coupling them with the side chains.



I R = C_6H_5

II R = $COOC_2H_5$

III R = CH_2OH

IV R = CHO

V R = $CH(CH_3)_2$

6-Methoxy-4-phenyl-8-aminoquinoline (I) was prepared by condensing *beta*-chloropropiophenone with *p*-methoxy-*o*-nitroaniline, and reducing the nitroquinoline catalytically or with stannous chloride. The *beta*-chloropropiophenone required for this synthesis was originally prepared by the procedure of Allen and Barker (3), but as the yields were variable, and the reaction was frequently very vigorous, a modification was developed which avoided some of these difficulties. When *beta*-chloropropiophenone was condensed with *p*-methoxy-*o*-nitroaniline by the procedure used by Elderfield and co-workers (4) for the analogous 2-phenyl derivative, the yield of I was only 5–8%; this yield was raised to 30% by the use of Cellosolve as solvent. Attempts to couple I with 5-isopropylaminopentyl chloride by the usual procedure (5) failed to give an appreciable amount of product, and work on this phase had to be abandoned because the experimenter became allergic to *beta*-chloropropiophenone.

6-Methoxy-8-nitrolepidine was the starting material for the synthesis of II and for attempted synthesis of III, IV and V. The nitrolepidine was oxidized to the corresponding cinchoninic acid by the procedure of Turner, Mills, and Cope (6); this acid was then esterified and the ester reduced to give II. When II was

[1] Previous paper in this series, Campbell *et al.*, *J. Am. Chem. Soc.*, **69**, 1465 (1947).

[2] Eli Lilly Research Fellow, University of Notre Dame, 1946–1948. Present address: E. Bilhuber, Inc., Orange, New Jersey.

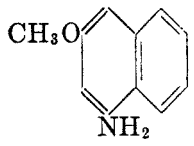
[3] Present address: Indiana University, South Bend, Indiana.

treated with Noval bromide or 1-isopropylamino-5-chloropentane the product was an oil which could not be distilled and from which we were unable to obtain any crystalline salt. Better results were obtained with diethylaminoethyl bromide, but as the product had no appreciable antimalarial activity no further efforts were made to prepare other drugs in this series.

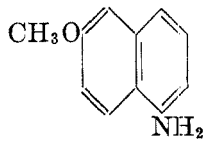
6-Methoxy-8-nitrolepidine was oxidized to the aldehyde by selenium dioxide, but all attempts to reduce 6-methoxy-8-nitrocinchonaldehyde to the amino alcohol (III), the amino aldehyde (IV) or the nitro alcohol gave only tars. It was hoped to prepare 6-methoxy-8-amino-4-isopropylquinoline (V) from 6-methoxy-8-nitrolepidine by condensation with formaldehyde followed by reduction. Although lepidine and 6-methoxylepidine react with formaldehyde to form the dimethylol compounds in good yields (7, 8) we were unable to isolate any appreable amount of methylol derivative from 6-methoxy-8-nitrolepidine, using aqueous formaldehyde, trioxane or paraformaldehyde.

A second phase of the work involved the attachment of other side chains to the 6-methoxy-8-aminolepidine nucleus. Alving (9) has found that 6-methoxy-8-(3′-isopropylaminopropylamino)lepidine is devoid of the Plasmocid type of toxicity so characteristic of most of the 8-aminoquinolines with short side chains; it therefore became of interest to prepare other 8-aminolepidines with short side chains. 6-Methoxy- and 6-hydroxy-8-(3′-*sec.*-butylaminopropylamino)lepidines were prepared, therefore, and the analogous quinolines without the 4-methyl group were also made for comparison. These syntheses were carried out in the usual way and presented no difficulties. 6-Methoxy-8-[bis-(dimethylaminomethyl)methylamino]lepidine was also desired for testing; 1,3-bis(dimethylamino)-2-propanol was prepared in excellent yield from dimethylamine and epichlorohydrin and converted to the chloro and bromo derivatives, but neither of these could be coupled with 6-methoxy-8-aminolepidine.

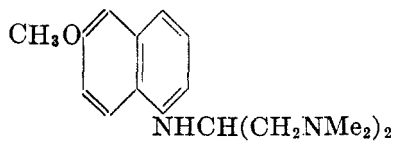
A third phase of the work was concerned with the preparation of naphthalene analogs of the 4- and 8-aminoquinolines. We originally planned to attach aminoalkylamino side chains to 3-methoxy-1-aminonaphthalene (VI) and to 6-methoxy-1-aminonaphthalene (VII), but we were not able to develop a satisfactory synthesis for VI in quantity. VII was readily prepared by a slight



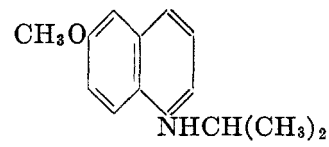
VI



VII



VIII



IX

modification of the procedure of Butenandt and Schramm (10). This nucleus

coupled readily with alkylaminoalkyl halides to give very good yields of the drugs, but as these products showed very slight antimalarial activity an extensive series was not made. Attempts to couple VII with 1,3-bis-(dimethylamino)-2-bromopropane were unsuccessful, and when the *p*-toluenesulfonate ester of 1,3-bis-(dimethylamino)-2-propanol was used the product was not the expected drug VIII, but may have been 6-methoxy-1-isopropylaminonaphthalene (IX). The mechanism by which the two dimethylamino groups were lost is obscure.

The antimalarial activities of the drugs prepared in this work are given in Table I. The authors wish to thank the Eli Lilly Company for carrying out the tests, and for the financial support which made this work possible.

TABLE I

ANTIMALARIAL ACTIVITY

COMPOUND	QUININE EQUIVALENTS TEST I-5
8-(3′-*sec.*-Butylaminopropylamino)-6-hydroxyquinoline	Q = 4
8-(3′-*sec.*-Butylaminopropylamino)-6-hydroxylepidine	Q = 0.16i
6-Methoxy-8-(3′-*sec.*-butylaminopropylamino)quinoline	Q = 0.16
6-Methoxy-8-(3′-*sec.*-butylaminopropylamino)lepidine	Q = 80
1-(4′-Isopropylamino-1′-methylbutylamino)-6-methoxynaphthalene	Q = 0.16i
1-(5′-Isopropylaminopentylamino)-6-methoxynaphthalene	Q = 0.16i
Ethyl 8-(2′-diethylaminoethylamino)-6-methoxycinchoninate	Q = 0.16i

EXPERIMENTAL[4,5]

beta-Chloropropiophenone. This material was prepared by a modification of the procedure of Allen and Barker (3). A mixture of 50 g. of *beta*-chloropropionic acid (11) and 45 g. of phosphorus trichloride was refluxed on a water-bath for 90 minutes, cooled, diluted with 200 ml. of dry benzene and decanted into a one-liter, three-neck flask fitted with a sealed stirrer and a reflux condenser which was protected by a calcium chloride drying tube. Seventy-five grams of anhydrous aluminum chloride was added in small portions over a period of two hours, each addition being accompanied by the evolution of heat and hydrogen chloride. The solution remained light yellow in color until addition was nearly complete, at which point a deep red color developed. When addition was completed the reaction mixture was refluxed on a water-bath for one hour, cooled, and poured into ice with good stirring. The organic layer was separated, washed with 100 ml. of water, dried over calcium chloride, and the benzene evaporated in a stream of dry air without the application of heat; the yield was 65.3 g. or 85% of a white solid, m.p. 46–48°. This product was recrystallized by dissolving in Skellysolve "B" at room temperature, cooling to 0° and filtering off the white plates, m.p. 47–48°.

4-Phenyl-6-methoxy-8-nitroquinoline. A mixture of 57.0 g. of 2-nitro-4-methoxyaniline, 51.0 g. of arsenic pentoxide, 51.0 g. of zinc chloride and 700 ml. of concentrated hydrochloric acid was heated on a steam-bath and a solution of 110 g. of *beta*-chloropropiophenone dissolved in 215 ml. of Cellosolve was added dropwise with stirring over a period of five hours. Heating and stirring were continued for one hour longer. Tetrachloroethane

[4] All melting points are uncorrected. The melting points of all salts were determined in sealed tubes and the samples were placed in the melting point block at room temperature.

[5] All analyses for C, H, and N were performed by Mr. Charles Beazley, Micro-Tech Laboratory, Skokie, Illinois.

(200 ml.) was added and the reaction mixture was allowed to cool and separate into two layers. The aqueous layer was decanted, the tarry organic layer was washed with two 100-ml. portions of concentrated hydrochloric acid and the combined acid solutions were then diluted with water to 9–10 times their original volume and allowed to stand overnight. The long, reddish needles which precipitated were recrystallized from 95% ethyl alcohol. Yield 24.0 g. or 30%; m.p. 129–134°. Repeated recrystallization from 95% ethanol yielded light tan needles, m.p. 133.5–135°.

Anal. Calc'd for $C_{16}H_{12}N_2O_2$: C, 68.56; H, 4.24; N, 10.00.
Found: C, 68.02; H, 4.15; N, 10.20.

4-Phenyl-6-methoxy-8-aminoquinoline. (A) *By reduction with stannous chloride.* A solution of 16.9 g. of stannous chloride dihydrate in 50 ml. of concentrated hydrochloric acid was cooled to 5° and a solution of 5.0 g. of 4-phenyl-6-methoxy-8-nitroquinoline in 40 ml. of concentrated hydrochloric acid was added dropwise, with stirring, over a period of one hour. The reaction mixture was then stirred at 0–5° for one hour and at room temperature for 90 minutes. Sodium hydroxide (40%) was added to strong alkalinity while the temperature was kept below 20°; at this point the tin salt was completely dissolved. The product, a dark brown solid, was collected and dried *in vacuo;* yield 5.6 g. (theoretical yield 4.5 g.), but combustion tests indicated the presence of inorganic salts. Distillation of this solid gave 3.2 g. (67%) of an extremely viscous, pale yellow oil, b.p. 178–192°/0.1 mm., which solidified on trituration with hexane and then had m.p. 74–77°. This product gave a negative Beilstein test indicating that no nuclear chlorination had occurred on treatment with stannous chloride.

Anal. Calc'd for $C_{16}H_{14}N_2O$: C, 76.83; H, 5.62; N. 11.17.
Found: C, 76.32; H, 5.54; N, 11.33.

(B) *By catalytic hydrogenation.* A solution of 5.6 g. (0.02 mole) of 4-phenyl-6-methoxy-8-nitroquinoline in 60 ml. of anhydrous ethyl acetate and 20 ml. of absolute ethanol was shaken with Raney nickel at room temperature under 3 atmospheres of hydrogen. The theoretical amount of hydrogen was absorbed in one hour. The residue was a dark, very viscous oil which on trituration with hexane crystallized to a gray solid, m.p. 71–74°; yield 4.4 g. or 88%.

Ethyl 6-methoxy-8-nitrocinchoninate. The 6-methoxy-8-nitrocinchoninic acid used in this work was prepared by the method of Turner, Mills, and Cope (6). A mixture of 54.0 g. of 6-methoxy-8-nitrocinchoninic acid, 800 ml. of anhydrous benzene, and 200 ml. of freshly distilled thionyl chloride was heated to reflux on a water-bath for six hours and was allowed to stand overnight. A total of 500 ml. of absolute ethanol was added through the top of the condenser in small portions with shaking. After the spontaneous reaction had subsided, the reaction mixture was refluxed on a water-bath for three hours, cooled, and filtered to remove a small amount of insoluble material. The filtrate was evaporated to dryness under reduced pressure with heating on a water-bath. Recrystallization of the residue from 95% ethyl alcohol yielded 46.0 g. or 76% of a light tan solid, m.p. 133–134°. Treatment of a small portion with decolorizing charcoal followed by two recrystallizations from 95% ethyl alcohol yielded fine, pale yellow needles, m.p. 142°.

Anal. Calc'd for $C_{13}H_{12}N_2O_5$: C, 56.52; H, 4.38; N, 10.14.
Found: C, 56.89; H, 4.00; N, 9.93.

Ethyl 6-methoxy-8-aminocinchoninate. A mixture of 37.5 g. (0.14 mole) of ethyl 6-methoxy-8-nitrocinchoninate, 32.0 g. of iron filings (Eastman Kodak, 40 mesh), 600 ml. of water, and 20 ml. of glacial acetic acid was stirred on a water-bath for fourteen hours, cooled, and filtered. The filter cake was leached out with 500 ml. of boiling dioxane and filtered while hot. Evaporation of the solvent under reduced pressure at 50° yielded a reddish-orange solid. No appreciable amount of product was obtained on further extraction of the filter cake. After one crystallization from 95% ethyl alcohol there was obtained 22.6 g. or 68% of an orange solid, m.p. 99–102°. This compound distilled at 162–167°/0.15 mm. to yield a clear red oil which soon solidified to yellow crystals, m.p. 108–109°.

Anal. Calc'd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38.

Found: C, 62.8; H, 5.49; N, 11.46.

Ethyl 6-methoxy-8-(2'-diethylaminoethylamino)cinchoninate. A solution of 24.6 g. (0.1 mole) of ethyl 6-methoxy-8-aminocinchoninate and 13.0 g. (0.05 mole) of *beta*-diethylaminoethyl bromide hydrobromide in 75 ml. of absolute ethanol was heated to reflux for 48 hours. The alcohol was removed under reduced pressure with a minimum of warming in a water-bath. The residue, a viscous dark red oil, was stirred vigorously with 200 ml. of cold water and the yellow solid which separated was collected. It proved to be 7.6 g. of unchanged ethyl 6-methoxy-8-aminocinchoninate, m.p. 102–104°. The filtrate was extracted with 100-, 100-, and 50-ml. portions of chloroform and the combined extracts were dried over potassium carbonate. The dark red residue remaining after evaporation of the solvent was distilled under vacuum to give an oil, (b.p. 200–215°/0.4 mm.) which was dissolved in 30 ml. of ice-cold 6 *N* hydrochloric acid. The acid solution was extracted with three 100-ml. portions of ether and the aqueous layer was slowly neutralized in the cold by the addition of solid potassium carbonate. When the evolution of carbon dioxide had ceased, 10% sodium hydroxide solution was added to *p*H 10. The cold solution was extracted rapidly with three 100-ml. portions of ether and the combined extracts were dried over potassium carbonate. After removal of the drying agent the solution was chilled in an ice-bath and treated with a saturated ethereal solution of anhydrous oxalic acid which was added dropwise from a burette with vigorous stirring. It was found essential to add the oxalic acid solution very slowly and to avoid the presence of an excess at any time in order to isolate a stable salt. When precipitation was complete the orange-yellow solid was collected and dried *in vacuo*. Recrystallization from absolute ethanol yielded 6.0 g. or 28% of orange-yellow plates, m.p. 146–147°. On analysis this salt proved to be a monooxalate.

Anal. Calc'd for $C_{21}H_{29}N_3O_7$: C, 58.05; H, 6.50; N, 9.67.

Found: C, 58.28; H, 6.69; N, 9.52.

6-Methoxy-8-nitrocinchoninaldehyde. A mixture of 60.0 g. of 6-methoxy-8-nitrolepidine, 46.0 g. of freshly prepared and sublimed selenium dioxide, 400 ml. of chlorobenzene, and 100 ml. of glacial acetic acid was refluxed for 48 hours and filtered from the selenium metal while still hot. The filtrate was evaporated to dryness at the water-pump with a minimum of heating. The residue, a reddish solid, was dissolved in 500 ml. of dioxane, refluxed with decolorizing charcoal and filtered hot through a mat of Hyflo Super-Cel. On cooling, a light tan solid, m.p. 183–185°, (50.4 g., 79%) separated from the filtrate. A small sample was recrystallized three times from dioxane and once from a 1:1 mixture of dioxane and 95% ethyl alcohol. The product was an almost colorless, fluffy solid which melted at 192°, decolorized potassium permanganate solution and gave an addition compound with sodium bisulfite.

Anal. Calc'd for $C_{11}H_8N_2O_4$: C, 56.90; H, 3.47; N, 12.07.

Found: C, 57.46; H, 3.53; N, 11.96.

1-sec.-Butylamino-3-propanol. A solution of 100 g. (1.05 moles) of trimethylene chlorohydrin and 200 g. (2.7 moles) of *sec.*-butylamine in 300 ml. of benzene was heated in an iron bomb for 9 hours. The residue remaining after removal of the benzene was treated with a solution of 42 g. of sodium hydroxide in 50 ml. of water and extracted with two 500-ml. portions of ether. The combined extracts were dried over potassium carbonate, the ether removed and the residue distilled to give 108 g. or a 78% yield of a colorless oil, b.p. 105°/20 mm., n_D^{20} 1.4490.

1-sec.-Butylamino-3-bromopropane hydrobromide. The method described by Campbell and co-workers (11) for the preparation of 1-alkylamino-6-bromohexanes from the corresponding amino alcohols was found to be very satisfactory. The yield of light tan crude material was 85%. After one recrystallization from ethanol and ether the product was a colorless, crystalline solid, m.p. 189–190° (dec.).

Anal. Calc'd for $C_7H_{17}Br_2N$: C, 30.57; H, 6.23; N, 5.09.

Found: C, 30.60; H, 6.02; N, 4.98.

6-Methoxy-8-(3'-sec.-butylaminopropylamino)quinoline. A mixture of 34.8 g. (0.20 mole) of freshly distilled 6-methoxy-8-aminoquinoline, 27.5 g. (0.10 mole) of 1-*sec.*-butyl-

amino-3-bromopropane hydrobromide and 300 ml. of absolute ethanol was refluxed for 48 hours, cooled, and filtered to remove the precipitated 6-methoxy-8-aminoquinoline hydrobromide. The filtrate was concentrated to a small volume under reduced pressure and was poured into a solution of 30 ml. of concentrated hydrochloric acid in 210 ml. of water. The acid solution was chilled in an ice-bath and sodium hydroxide pellets were added slowly, with stirring, to strong alkalinity. The solution was extracted with 100- and 50-ml. portions of chloroform and the combined extracts were dried over magnesium sulfate. After removal of the chloroform the dark, viscous residue was distilled from a 50-ml. Claisen flask with a low, wide side arm to give 15.4 g. (53%) of a viscous, red oil, b.p. 170–173°/0.08 mm. The oil was dissolved in 25 ml. of *n*-propanol and titrated with a slight excess of the amount of 2.017 *N* propanolic hydrogen chloride required to form the dihydrochloride. The yellow salt precipitated on cooling. After one recrystallization from ethanol and ether this material melted at 207.5–208.5° (dec.). It analyzed as a hemihydrate.

Anal. Calc'd for $C_{17}H_{25}N_3O \cdot 2HCl \cdot \frac{1}{2}H_2O$: C, 55.28; H, 7.64; N, 11.38.
Found: C, 55.60; H, 7.48; N, 11.67.

6-Methoxy-8-(3′-sec.-butylaminopropylamino)lepidine. This was prepared as described above using 17.9 g. (0.065 mole) of 1-*sec.*-butylamino-3-bromopropane hydrobromide, 24.4 g. (0.13 mole) of 6-methoxy-8-aminolepidine, and 200 ml. of absolute ethanol. There was obtained 9.2 g. (47%) of a viscous red oil, b.p. 180–184°/0.03 mm., which was converted to the dihydrochloride in propanol. The orange-yellow salt, m.p. 219–220° (dec.), analyzed as a hemihydrate.

Anal. Calc'd for $C_{18}H_{27}N_3O \cdot 2HCl \cdot \frac{1}{2}H_2O$: C, 56.39; H, 7.89; N, 10.96.
Found: C, 56.10; H, 7.77; N, 11.09.

6-Hydroxy-8-(3′-sec.-butylaminopropylamino)lepidine. A solution of 11.2 g. (0.037 mole) of 6-methoxy-8-(3′-*sec.*-butylaminopropylamino)lepidine in 100 ml. of constant boiling 48% hydrobromic acid was heated at 110° ± 2° (inside temperature) in a current of nitrogen for three and one-half hours. The reaction mixture was cooled to 15° in an ice-bath and 25% sodium hydroxide solution was added, under an atmosphere of nitrogen, to *p*H 9.5. The product separated as a dark red tar which adhered to the sides of the flask. The aqueous phase was decanted and the residual tar was dissolved in 20 ml. of absolute ethanol. Acidification with propanolic hydrogen chloride followed by the addition of ether precipitated the hydrochloride as a red oil, which was triturated with four successive portions of acetone to remove the last traces of water. After extensive scratching under anhydrous ether the oil was induced to crystallize to a yellow solid, m.p. 194–196° (dec.) after softening at 186–188°; the yield of crude material 7.9 g. or 54%. Recrystallization from methanol and ether raised the melting point to 200–202° (dec.), but the material was still contaminated with inorganic salts. It was therefore dissolved in the minimum amount of water, neutralized with solid sodium carbonate and extracted with chloroform. The dried chloroform extract was acidified with a slight excess of propanolic hydrogen chloride, and the addition of ether precipitated the yellow hydrochloride, m.p. 220–222° (dec.). This derivative was free from ash and analyzed as the dihydrochloride hemihydrate.

Anal. Calc'd for $C_{17}H_{25}N_3O \cdot 2HCl \cdot \frac{1}{2}H_2O$: C, 55.28; H, 7.64; N, 11.38.
Found: C, 55.26; H, 7.51; N, 11.30.

8-(3′-sec.-Butylaminopropylamino)-6-quinolinol. A solution of 12.0 g. of 6-methoxy-8-(3′-*sec.*-butylaminopropylamino)quinoline dihydrochloride hemihydrate in 100 ml. of constant boiling 48% hydrobromic acid was heated at 110° ± 2° for three hours in a stream of nitrogen. When the reaction mixture was allowed to cool slowly the product separated as fine, light tan needles which were collected and washed thoroughly with acetone and anhydrous ether; yield 13.0 g. or 77%; m.p. 207–208° (dec.). Analysis showed the salt to be a trihydrobromide.

Anal. Calc'd for $C_{16}H_{23}N_3O \cdot 3HBr$: C, 37.23; H, 5.08; N, 8.14.
Found: C, 37.23; H, 5.10; N, 8.42.

5-Acetylamino-2-naphthol. This compound was prepared in 42% yield by the procedure of Butenandt and Schramm (10). By the procedure described below yields as high as 82%

were obtained. The fusion pot was a stainless steel beaker (7.8 cm. in diameter and 11.2 cm. deep) equipped with a removable stainless steel cover and fitted with a stainless steel propellor type stirrer and powerful motor. The pot was charged with 140 g. of potassium hydroxide pellets and 10 ml. of water and was heated to 250° in a Wood's metal-bath. Sixty grams of 1-naphthylamine-6-sulfonic acid (Cleve's acid, duPont technical grade) was added in three portions and the mass was heated rapidly to 310° and maintained at 310–320° for no longer than eight minutes and for an even shorter period if the odor of ammonia became apparent above the fusion pot before that time. The melt was cooled and dissolved in 250 ml. of boiling water. The results of three fusions were combined, made strongly acid to pH paper with ice cold 6 *N* hydrochloric acid and filtered. The filter cake was leached out with a solution of 70 ml. of concentrated hydrochloric acid in 1000 ml. of water and filtered. This process was repeated four times, at which point the insoluble residue was small and tarry in nature. The combined filtrates were cooled and potassium hydroxide pellets were added to turbidity. A saturated solution of ammonium carbonate was then added until no more precipitate formed. The brown solid was collected and dried in a vacuum desiccator overnight. Acetic anhydride (300 g.) was added cautiously to the slightly moist material (160 g.) which was cooled in an ice-bath. After the initial mildly exothermic reaction had subsided, the mixture was stirred at room temperature for 3 hours and the light tan solid collected and dried in air; yield 134 g. or 82%, m.p. 211–213°.

6-Methoxy-1-naphthylamine. This was prepared from 5-acetylamino-2-naphthol by the procedure of Butenandt and Schramm (10). These workers report m.p. 205–220° (dec.) for 6-methoxy-1-naphthylamine hydrochloride and m.p. 74° for the free base. Wilds and Close (12) report m.p. 255° (dec.) for the hydrochloride. The crude hydrochloride obtained in this work melted at 230–239° (dec.) and the free base melted 64–66°.

1-(5'-Isopropylaminopentylamino)-6-methoxynaphthalene. A mixture of 23.0 g. (0.133 mole) of 6-methoxy-1-naphthylamine, 12.2 g. (0.066 mole) of 1-isopropylamino-5-chloropentane hydrochloride, and 15 ml. of water was stirred and heated in an oil-bath at 85–90° for 20 hours and at 100° for an additional 4 hours. The hot reaction mixture was poured into a solution of 25 ml. of concentrated hydrochloric acid in 100 ml. of water. After cooling, the purple crystals of recovered 6-methoxy-1-naphthylamine hydrochloride were collected, the filtrate was chilled in an ice-bath and sodium hydroxide pellets were added to strong alkalinity. The basic solution was then extracted with two 100-ml. portions of chloroform, the combined extracts were dried over magnesium sulfate, and the chloroform was evaporated under reduced pressure with mild warming. Distillation of the residue gave a pale yellow oil, b.p. 190–195°/0.18 mm.; yield 15.0 g. or 75%. The oil was dissolved in 40 ml. of *n*-propanol and treated with propanolic hydrogen chloride; the dihydrochloride was precipitated by the cautious addition of anhydrous ether. It had a slight greenish cast and the m.p. 214–216° (dec.). After one recrystallization from ethanol and ether this compound retained its pale green tint and melted at 216–218° (dec.).

Anal. Calc'd for $C_{19}H_{28}N_2O \cdot 2HCl$: C, 61.12; H, 8.12; N, 7.50.
Found: C, 60.70; H, 8.01; N, 7.52.

1-(4'-Isopropylamino-1'-methylbutylamino)-6-methoxynaphthalene. This was prepared in the same way, using 14.7 g. (0.085 mole) of 6-methoxy-1-naphthylamine, 12.5 g. (0.043 mole) of 1-isopropylamino-4-bromopentane hydrobromide, and 15 ml. of water; yield 6.8 g. or 53% of a viscous, pale yellow oil, b.p. 185–187°/0.15 mm. The dihydrochloride, prepared in propanol, precipitated as an oil on the addition of dry ether. It was crystallized with difficulty by scratching under successive portions of fresh ether. After drying *in vacuo* this compound had no melting point but began to decompose at 108°.

Anal. Calc'd for $C_{19}H_{28}N_2O \cdot 2HCl \cdot \frac{1}{2}H_2O$: C, 59.68; H, 8.17; N, 7.33.
Found: C, 59.46; H, 7.88; N, 6.83.

From mixtures of methanol, ethanol, or propanol and ether, the hydrochloride separated as an oil which could not be crystallized. Recrystallization from chloroform and ether yielded a yellow solid, m.p. 179–182° (dec.), which was shown by analysis to contain slightly

less than one molar equivalent of chloroform. Trituration with hexane followed by drying for 24 hours in a vacuum desiccator and for six hours in an Abderhalden pistol at 77° and 2 mm. failed to remove the chloroform.

1,3-Bis-(dimethylamino)-2-propanol. One mole (92.5 g.) of epichlorohydrin was added at the rate of 3–4 drops per second, with vigorous stirring, to 800 g. of 40% dimethylamine solution. The reaction was exothermic and the inside temperature had risen to 70° by the time addition was completed. The reaction mixture was stirred at 90° for 6 hours and then allowed to stand overnight. The mixture was chilled in an ice-bath and saturated with sodium hydroxide; the yellow organic layer which separated was dried over sodium hydroxide. Distillation through a short Vigreux column yielded 96.9 g. or 66% of a colorless oil, b.p. 82°/23 mm., 90°/32 mm., 98°/48 mm., n_D^{20} 1.4418, d_4^{20} 0.8788, MR_D (calc'd), 43.95; MR_D (obs.), 43.98; neutral equivalent (calc'd) 73.0; neutral equivalent (obs.), 73.3. The amino alcohol readily formed a dihydrochloride m.p. 255–257° (dec.), and a dihydrobromide, m.p. 228–230° (dec.).

1,3-Bis-(dimethylamino)-2-bromopropane hydrobromide. A solution of 66.5 g. (0.45 mole) of 1,3-bis-(dimethylamino)-2-propanol in 250 ml. of dry benzene was cooled below 10° and 97.0 g. (0.47 mole) of freshly distilled thionyl bromide was added dropwise with mechanical stirring over a period of two hours. When the addition was complete the mixture was stirred at 10° for 30 minutes and at room temperature for an hour. The cream colored solid was washed well with anhydrous ether and dried *in vacuo*. Yield 81.3 g. or 62%. An almost colorless solid, m.p. 187–189° (dec.) after softening at 167–169°. This material was hygroscopic and turned to an oil on exposure to the air for about 10 minutes.

Anal. Calc'd for $C_7H_{17}BrN_2 \cdot HBr$: C, 28.98; H, 6.25; N, 9.66.
Found: C, 28.82; H, 6.19; N, 9.28.

1,3-Bis-(dimethylamino)-2-propyl p-toluenesulfonate hydrochloride. A solution of 65.0 g. (0.34 mole) of *p*-toluenesulfonyl chloride in 300 ml. of chloroform was cooled in an ice-bath and 44.8 g. (0.31 mole) of 1,3-bis-(dimethylamino)-2-propanol was added over a period of 90 minutes while the temperature was kept below 20°. The mixture was stirred at room temperature for two hours after the addition was complete and was filtered. The product was somewhat oily in nature but crystallized well when stirred with anhydrous ether. After drying in a vacuum desiccator there was obtained 65.8 g. or 64% of a white powder. The analytical sample was recrystallized from ethanol and ether and was obtained as white plates, m.p. 166–167° (dec.). The product analyzed as a hemihydrate.

Anal. Calc'd for $C_{14}H_{25}N_2O_3S \cdot \frac{1}{2}H_2O$: C, 48.61; H, 7.58; N, 8.11.
Found: C, 48.50; H, 7.48; N, 7.62.

Reaction of 6-methoxy-1-naphthylamine with 1,3-bis-(dimethylamino)-2-propyl p-toluenesulfonate hydrochloride. A mixture of 21.0 g. (0.12 mole) of 6-methoxy-1-naphthylamine, 17.3 g. (0.05 mole) of 1,3-bis-(dimethylamino)-2-propyl *p*-toluenesulfonate hydrochloride hemihydrate, 150 ml. of chloroform, and 50 ml. of acetone was refluxed for 24 hours. The amine dissolved rapidly and the sulfonate ester formed a milky suspension. At the end of the heating period the milkiness had disappeared and a flocculent gray solid had separated. The gray solid was removed by filtration from the cold mixture; it proved to be largely unreacted *p*-toluenesulfonate. The filtrate was concentrated to a small volume and the residue was stirred vigorously with 10% sodium hydroxide solution. The dark organic layer was separated, the aqueous phase was extracted with two 50-ml. portions of chloroform and the combined organic layers were dried over magnesium sulfate. Distillation of the residue remaining after removal of the chloroform gave two fractions. The first one, b.p. 130–145°/0.4 mm., was a mixture which could not be separated into its components. The second fraction, b.p. 145–155°/0.45 mm., was a pale yellow oil (2.5 g.) which formed a hydrochloride m.p. 199–200° (dec.). Analysis showed that it was not the desired product but may have been 1-isopropylamino-6-methoxynaphthalene hydrochloride.

Anal. Calc'd for $C_{18}H_{27}N_3O \cdot 3HCl$: C, 52.62; H, 7.36; N, 10.23.
Calc'd for $C_{18}H_{27}N_3O \cdot 2HCl$: C, 57.75; H, 7.81; N, 11.23.

Calc'd for 1-isopropylamino-6-methoxynaphthalene hydrochloride, $C_{14}H_{17}NO \cdot HCl$: C, 66.79; H, 7.21; N, 5.57.

Found: C, 67.80; H, 6.99; N, 5.55.

SUMMARY

1. The synthesis of several 6-substituted-8-aminolepidines and related compounds has been described.

2. Some 6-methoxy-1-aminonaphthalene derivatives have also been prepared as possible antimalarials.

3. The antimalarial activities of these compounds have been determined.

NOTRE DAME, IND.

REFERENCES

(1) CAMPBELL *et al.*, *J. Am. Chem. Soc.*, **68**, 1556 (1946).
(2) CAMPBELL *et al.*, *J. Am. Chem. Soc.*, **69**, 1465 (1947).
(3) ALLEN AND BARKER, *J. Am. Chem. Soc.*, **54**, 740 (1932).
(4) ELDERFIELD *et al.*, *J. Am. Chem. Soc.*, **68**, 1590 (1946).
(5) ELDERFIELD *et al.*, *J. Am. Chem. Soc.*, **68**, 1524 (1946).
(6) TURNER, MILLS, AND COPE, *J. Am. Chem. Soc.*, **68**, 2222 (1946).
(7) KOENIGS, *Ber.*, **31**, 2371 (1898).
(8) CAMPBELL AND SCHAFFNER, unpublished work.
(9) ALVING, private communication.
(10) BUTENANDT AND SCHRAMM, *Ber.*, **68B**, 2083 (1935).
(11) CAMPBELL *et al.*, *J. Am. Chem. Soc.*, **68**, 1556 (1946).
(12) WILDS AND CLOSE, *J. Am. Chem. Soc.*, **69**, 3080 (1947).