[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF DEPAUW UNIVERSITY]

POTENTIAL ANTIMALARIAL COMPOUNDS IN THE α-(1-DIALKYLAMINOETHYL)-1-NAPHTHALENE-METHANOL SERIES[1]

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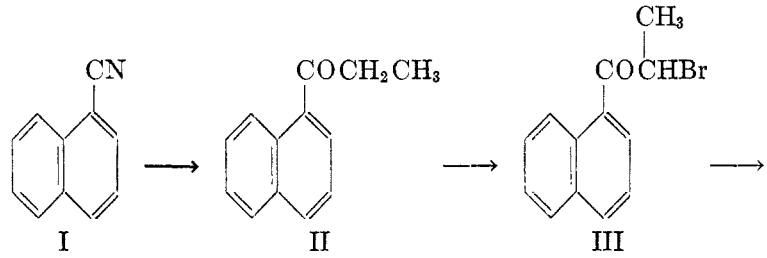
The preparation of potential antimalarial substances of type V was undertaken, at the suggestion of the malaria unit at the National Institute of Health, as part of a program of synthesis of amino alcohols containing the naphthalene nucleus.

1-Naphthonitrile served as a convenient starting material for the proposed synthesis. By reaction with ethylmagnesium bromide this nitrile (I) gave 1-propionylnaphthalene (II) in 85–90% yields. Bromination of 1-propionylnaphthalene in anhydrous ether solution at 10° afforded a solid bromo ketone (79–85% yields of pure material) which yielded 1-naphthoic acid upon oxidation with sodium hypochlorite. Since the identical bromo ketone was obtained from the reaction of naphthalene with α-bromopropionyl bromide, its structure was established as III.

1-(α-Bromopropionyl)naphthalene (III) in ether solution reacted slowly at room temperature with piperidine, dimethylamine, diethylamine, di-*n*-propylamine, and di-*n*-butylamine to yield amino ketones of type IV. In two instances (NR_2 = piperidino and dimethylamino) the amino ketones were isolated as crystalline hydrochlorides. Usually, however, the crude, relatively unstable, liquid amino ketone was reduced directly with aluminum isopropoxide in a nitrogen atmosphere. The amino alcohols (V) obtained in this manner were isolated as crystalline hydrochlorides in over-all yields of 25–68% from bromo ketone III. α-(1-Piperidinoethyl)-1-naphthalenemethanol (V, NR_2 = piperidino) was also isolated as the crystalline free base.



[1] The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and DePauw University. 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 a number has been assigned will be tabulated in a forthcoming monograph.

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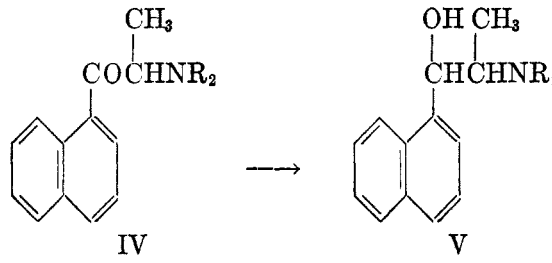

IV V

EXPERIMENTAL

1-Propionylnaphthalene (II)[3]. To the Grignard reagent prepared from 16.2 g. of magnesium, 80 g. of ethyl bromide, and 200 cc. of ether was added with constant swirling 86.4 g. of 1-naphthonitrile in 200 cc. of ether. The clear brown solution was refluxed gently for eighteen hours (precipitation of solid yellow complex) and was then hydrolyzed with ice and hydrochloric acid. The ethereal layer was separately refluxed with 100 cc. of 10% hydrochloric acid, while the original aqueous layer was heated on the steam-bath for one-half hour. The combined hydrolysis mixtures were separated and the aqueous layer extracted with ether. Upon evaporation, the combined ether extracts yielded a dark oil which was distilled in vacuum; yield, 90 g. (89%) of colorless 1-propionylnaphthalene; b.p. 144–146° at 1 mm. Hartung, Munch, and Crossley (1) reported a 68% yield of 1-propionylnaphthalene from the reaction of ethylmagnesium bromide and 1-naphthonitrile. This ketone has also been obtained, along with the 2-isomer, from the reaction of propionyl chloride with naphthalene (2).

1-Propionylnaphthalene yielded a picrate, m.p. 78–79°. Rousset (2) reported the m.p. 77–78° for this picrate.

1-(α-Bromopropionyl)naphthalene (III). (*a*) *From 1-propionylnaphthalene.*[3] To a stirred solution of 92 g. of 1-propionylnaphthalene in 500 cc. of anhydrous ether was added dropwise 80 g. of bromine. The bromination was begun at room temperature, but was carried out at 10° for the major portion of the addition. The bromo ketone which had crystallized during the bromination was brought back into solution by the addition of benzene and the reaction mixture was then washed with 10% sodium bisulfite and with water. The dried organic layer was evaporated to a volume of about 300 cc., 200 cc. of hot petroleum ether (b.p. 60–75°) was added, and the solution was allowed to cool. Pure bromo ketone crystallized (88 g.); m.p. 88–89°. By working up the mother liquor, an additional quantity (21 g.) of the same purity was obtained; total yield, 109 g. (83%).

(*b*) *From naphthalene and α-bromopropionyl bromide.* To a mechanically-stirred mixture of α-bromopropionyl bromide (24.6 g., freshly-distilled), naphthalene (14.6 g.), and carbon disulfide (150 cc.) which was cooled in an ice-salt bath, was added anhydrous aluminum chloride (18.3 g., finely powdered) over a period of twenty minutes. The reaction mixture was then allowed to stand at 0° for four hours and at room temperature for twenty-four hours, and was finally hydrolyzed with ice and hydrochloric acid. Two hundred cc. of ether was added to the hydrolyzed mixture, the layers were separated and the organic layer was washed with water and dried. Upon concentrating and cooling the ethereal solution, crude *1-(α-bromopropionyl)naphthalene* crystallized, and was purified by crystallization from ether; yield, 8–10 g. (27–33%) melting at 88–89° alone and also when mixed with a sample of bromo ketone prepared from 1-propionylnaphthalene.

Anal. Calc'd for $C_{13}H_{11}BrO$: C, 59.33, H, 4.21.

Found: C, 59.00; H, 4.16.

A mixture of 2 g. of 1-(α-bromopropionyl)naphthalene, 12 cc. of 5% sodium hypochlorite solution and 0.4 g. of potassium hydroxide was refluxed for three hours, and was then distilled as long as water-insoluble material came over. When the residual solution was treated with charcoal, filtered, and acidified with hydrochloric acid, there was precipitated

[3] Prepared by Emma Ruth Hornor.

1.0 g. of *1-naphthoic acid*, m.p. 157–159°. One recrystallization of this material from ethanol yielded colorless needles, m.p. 160–161°, which were identified as 1-naphthoic acid by mixed m.p. determination.

Synthesis of α-(1-piperidinoethyl)-1-naphthalenemethanol. (*a*) *1-(α-Piperidinopropionyl)naphthalene* (*IV*, NR_2 = *piperidino*). When a solution of 10 g. of 1-(α-bromopropionyl)naphthalene in 100 cc. of anhydrous ether was added to a solution of 6.5 g. (2 moles) of piperidine in 25 cc. of anhydrous ether, the mixture soon became cloudy due to precipitation of piperidine hydrobromide. The solution was allowed to stand in the dark in a stoppered flask at room temperature for four days before being filtered from piperidine hydrobromide (5.1 g. or 80%). The ethereal solution was then washed with 50 cc. of 10% sodium hydroxide, then with water, and was finally extracted with two 100-cc. portions of 10% hydrochloric acid. The combined acid extracts were neutralized with sodium hydroxide and the precipitated keto amine was extracted with ether. To the dried ethereal extract was added dropwise a solution of anhydrous hydrogen chloride in anhydrous ether until no further precipitation resulted. The precipitated *1-(α-piperidinopropionyl)naphthalene hydrochloride* weighed 7.7 g. (67% yield); m.p. 213–215°. One recrystallization of this material from anhydrous ethanol-ether yielded 5.5 g. of colorless needles, m.p. 218–219°.

(*b*) *α-(1-Piperidinoethyl)-1-naphthalenemethanol* (*V*, NR_2 = *piperidino*). The amino ketone regenerated from 5.5 g. of the aforementioned hydrochloride by means of sodium hydroxide was reduced in an atmosphere of nitrogen by refluxing with 3.7 g. of aluminum isopropoxide (vacuum-distilled) and 20 cc. of anhydrous isopropyl alcohol, slowly distilling off the acetone and part of the isopropyl alcohol, adding fresh alcohol, and repeating the process until no more acetone could be detected in the distillate with 2,4-dinitrophenylhydrazine test solution (about three hours). To the cooled reduction mixture, from which the bulk of the isopropyl alcohol had been distilled, was added 6 cc. of 10 *N* sodium hydroxide solution to decompose the complex, followed by ether to dissolve the free amino alcohol. The layers were separated and the aqueous layer was extracted a second time with ether. The combined ethereal extracts were extracted twice with 15-cc. portions of 10% hydrochloric acid and the acid extracts were decolorized with charcoal. Upon evaporation of the acidic solution to a small volume there was obtained 3.84 g. (70% yield) of *α-(1-piperidinoethyl)-1-naphthalenemethanol hydrochloride*, m.p. 226–231°. One crystallization of this material from anhydrous ethanol-ether yielded colorless needles, m.p. 244–245°.

Anal. Calc'd for $C_{18}H_{23}NO \cdot HCl$: C, 70.68; H, 7.91.
Found: C, 70.24; H, 7.91.

When an aqueous solution of the aforementioned hydrochloride was neutralized with sodium hydroxide, the free amino alcohol was precipitated as a colorless solid. *α-(1-Piperidinoethyl)-1-naphthalenemethanol* crystallizes from ethanol-water in colorless needles, m.p. 108–109°.

Anal. Calc'd for $C_{18}H_{23}NO$: C, 80.25; H, 8.60.
Found: C, 80.03; H, 8.30.

1-(α-Dimethylaminopropionyl)naphthalene (*IV*, *R* = *methyl*). When a solution of 10 g. of 1-(α-bromopropionyl)naphthalene in 100 cc. of anhydrous ether was added to a solution of 6.8 g. (4 moles) of anhydrous dimethylamine in 15 cc. of anhydrous ether, crystallization of dimethylamine hydrobromide began almost immediately, but no heat of reaction was evolved. The mixture was allowed to stand in the dark in a nitrogen atmosphere at room temperature for twenty hours, and the dimethylamine hydrobromide was filtered off: yield, 3.88 g., or 81%. The amino ketone solution was worked up in the manner previously described for the preparation of 1-(α-piperidinopropionyl)naphthalene hydrochloride: yield, 3.2 g. (32%) of crude hydrochloride, m.p. 200–210°. Three recrystallizations from anhydrous ethanol-ether raised the m.p. of *1-(α-dimethylaminopropionyl)naphthalene hydrochloride* to 215–216°.

Anal. Calc'd for $C_{15}H_{17}NO \cdot HCl$: C, 68.30; H, 6.88.
Found: C, 68.35; H, 6.92.

α-(1-Dimethylaminoethyl)-1-naphthalenemethanol (*V*, *R* = *methyl*; *SN-7728*). A solution

of 52.6 g. of 1-(α-bromopropionyl)naphthalene in 500 cc. of anhydrous ether was added to a solution of 36 g. (4 moles) of anhydrous dimethylamine in 50 cc. of anhydrous ether, the mixture was allowed to stand in the dark in an atmosphere of nitrogen at room temperature for twenty hours, and the dimethylamine hydrobromide was filtered off (20.4 g. or 81%). The yellow filtrate was washed with 100 cc. of 5% sodium hydroxide and twice with 50-cc. portions of water, and was dried briefly over calcium chloride. Evaporation of the ether under reduced pressure (finally employing a vacuum of 15 mm.) yielded a yellow oil which was reduced in an atmosphere of nitrogen according to the method of Meerwein and Ponndorf. Two hundred cc. of isopropyl alcohol and 40.8 g. of vacuum-distilled aluminum isopropoxide were employed, and the distillate contained no acetone after heating the reaction mixture for a period of nine hours.

The dark, semi-solid complex (volume about 120 cc.) which remained when the bulk of the isopropyl alcohol was distilled from the reduction mixture was decomposed by adding, with cooling, 60 cc. of 10 *N* sodium hydroxide. The aqueous solution was diluted with water and extracted several times with ether. To the dried (calcium chloride) ethereal extract was added dropwise, at room temperature, a solution of anhydrous hydrogen chloride in anhydrous ether, swirling vigorously throughout the addition. When the addition of a drop of the hydrogen chloride solution no longer caused any precipitation, the crude, chocolate-brown, crystalline *α-(1-dimethylaminoethyl)-1-naphthalenemethanol hydrochloride* was filtered off and air-dried; yield, 36 g. (68%). One crystallization from anhydrous methanol-ether yielded 24.7 g. (47%) of cream colored needles, m.p. 204–207° dec., and a second crystallization raised the m.p. to 207–210° dec. and removed all color.

Anal. Calc'd for $C_{15}H_{19}NO \cdot HCl$: Cl, 13.34. Found: Cl, 13.33

α-(1-Diethylaminoethyl)-1-naphthalenemethanol (*V*, *R* = *ethyl*; *SN-7729*). The reaction between 1-(α-bromopropionyl)naphthalene (72 g.) and diethylamine (80 g.) in ether (760 cc.) took place to the extent of 81% (on the basis of the quantity of diethylamine hydrobromide precipitated; 34 g.) when carried out under the conditions previously described for the reaction with dimethylamine. The brown-red ethereal solution of the keto amine was worked up as previously described, and the Meerwein-Ponndorf reduction was carried out in a nitrogen atmosphere for six and one-half hours, employing 56.4 g. of aluminum isopropoxide.

Precipitation of the crude amino alcohol hydrochloride with anhydrous hydrogen chloride in ether was carried out as before. At first the hydrochloride was precipitated as a finely-divided solid, but as precipitation neared completion the hydrochloride became gummy. Addition of hydrogen chloride was stopped at this point, and the solid hydrochloride (52 g. or 64.5%) was filtered off. Addition of hydrogen chloride to the filtrate yielded only a dark, oily product which could not be crystallized.

Two crystallizations of the *α-(1-diethylaminoethyl)-1-naphthalenemethanol hydrochloride* from anhydrous ethanol-ether yielded 30 g. (37%) of practically colorless crystals melting at 182–185° dec. One more crystallization raised the m.p. to 185–187° dec.

Anal. Calc'd for $C_{17}H_{23}NO \cdot HCl$: C, 69.48; H, 8.23.
Found: C, 69.08, H, 7.70.

The *4,4'-methylenebis-(3-hydroxy-2-naphthoic acid) salt of α-(1-diethylaminoethyl)-1-naphthalenemethanol* was precipitated in quantitative yield as a grey solid when a solution of 1.953 g. (1.95 moles) of 4,4'-methylenebis-(3-hydroxy-2-naphthoic acid) in 104 cc. of 0.1 *N* sodium hydroxide was added dropwise, with constant swirling, to a solution of 2.672 g. (1 mole) of α-(1-diethylaminoethyl)-1-naphthalenemethanol (prepared from the aforementioned hydrochloride by neutralizing an aqueous solution with sodium hydroxide) dissolved in 104 cc. of 0.1 *N* hydrochloric acid. The salt may be recrystallized from anhydrous ether-petroleum ether or from dioxane; yellow needles, m.p. 126° dec.

Anal. Calc'd for $C_{57}H_{62}N_2O_8$: N, 3.10. Found: N, 2.50.

α-(1-Di-n-propylaminoethyl)-1-naphthalenemethanol (*V*, *R* = *n-propyl*; *SN-8660*) was prepared from 65 g. of 1-(α-bromopropionyl)naphthalene and 99 g. of di-*n*-propylamine in the manner previously described for the dimethylamino analog. The reaction between the

bromo ketone and the di-*n*-propylamine took place to the extent of 85.5% within thirty days (38.5 g. of di-*n*-propylamine hydrobromide was filtered off). Ether and unreacted di-*n*-propylamine were then distilled in vacuum and the crude, oily, red-brown keto amine was reduced in a nitrogen atmosphere over a period of five hours, employing 50.4 g. of aluminum isopropoxide.

To the mixture of acetone and isopropyl alcohol distilled from the reduction was added 49 g. of 2,4-dinitrophenylhydrazine and 50 cc. of 36% hydrochloric acid. The mixture was heated to boiling, 200 cc. of hot water was added to the clear solution, and the solution was allowed to cool. There was obtained 48.3 g. of acetone 2,4-dinitrophenylhydrazone, m.p. 123–125°, indicating that the reduction had gone at least 82% to completion.

When anhydrous ethereal hydrogen chloride was added to the ether solution of the crude amino alcohol, *α-(1-di-n-propylaminoethyl)-1-naphthalenemethanol hydrochloride* was precipitated as an orange-brown gum. This material was dissolved in 200 cc. of water, and the solution was decolorized by first shaking several times with ether and finally treating with charcoal. Aqueous sodium hydroxide was added to precipitate the amino alcohol, which was extracted with ether. The amino alcohol hydrochloride was again precipitated from the dried ether solution by addition of ethereal hydrogen chloride. Cooling and rubbing the gummy hydrochloride with a little anhydrous methanol and ether sufficed to induce crystallization. There was finally obtained 19.7 g. (25% yield) of crystalline hydrochloride, which formed 17.9 g. of colorless prisms, m.p. 168–170°, when recrystallized from anhydrous methanol-ether.

Anal. Calc'd for $C_{19}H_{27}NO \cdot HCl$: Cl, 11.02. Found: Cl, 11.02.

α-(1-Di-n-butylaminoethyl)-1-naphthalenemethanol (*V*, *R* = *n-butyl*; *SN-8659*) was prepared from 10 g. of 1-(α-bromopropionyl)naphthalene and 20 g. of di-*n*-butylamine in the previously described manner. The bromo ketone reacted quantitatively with the di-*n*-butylamine within seventy days. Ether and unreacted di-*n*-butylamine were distilled from the crude, oily, orange-brown keto amine in vacuum. Meerwein-Ponndorf reduction in a nitrogen atmosphere was complete within four hours, employing 8.35 g. of aluminum isopropoxide, and 81% of the theoretical quantity of acetone 2,4-dinitrophenylhydrazone was recovered from the distillate in the manner previously described.

Addition of anhydrous ethereal hydrogen chloride to the ethereal solution of the crude amino alcohol precipitated *α-(1-di-n-butylaminoethyl)-1-naphthalenemethanol hydrochloride* in crystalline form; yield, 6.2 g. (47%). One crystallization from anhydrous methanol-ether yielded 5.2 g. of colorless needles, m.p. 135–137°.

Anal. Calc'd for $C_{21}H_{31}NO \cdot HCl$: Cl, 10.13. Found: Cl, 10.40.

SUMMARY

The synthesis of five α-(1-dialkylaminoethyl)-1-naphthalenemethanols has been described.

GREENCASTLE, IND.

REFERENCES

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