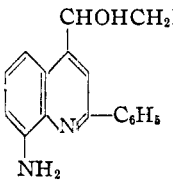
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

α-(Dialkylaminomethyl)-8-amino(or hydroxy)-4-quinolinemethanols[1]

BY RICHARD B. TURNER, JACK MILLS AND ARTHUR C. COPE

The α-(dialkylaminomethyl)-8-amino-2-phenyl-4-quinolinemethanols (I) described in the preceding paper[2] were found to have a low order of avian antimalarial activity, compared to the most active 4-quinolinemethanols or 8-aminoquinolines. Since a 2-phenyl substituent increases the antimalarial activity of 4-quinolinemethanols and decreases the activity of 8-aminoquinolines, it was of interest to prepare compounds similar to I but lacking the 2-phenyl group and compare the antimalarial activities of the two series.



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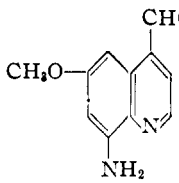
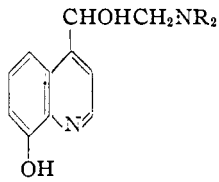


II a, R = ethyl
b, R = *n*-butyl
c, R = *n*-hexyl



III a, R = ethyl
b, R = *n*-butyl
c, R = *n*-hexyl

The compounds which were synthesized for comparison with I were the α-(dialkylaminomethyl)-8-amino-6-methoxy-4-quinolinemethanols (II). Three α-(dialkylaminomethyl)-8-hydroxy-4-quinolinemethanols (III) analogous to similar compounds substituted by a 2-phenyl group which are described in the preceding paper were also prepared.

The first synthetic work undertaken in this series consisted in preparation of the 8-hydroxy compounds (III). The synthesis began with 8-hydroxycinchoninic acid, which was obtained from cinchoninic acid by sulfonation and alkali fusion. 8-Acetoxycinchoninic acid was prepared by acetylation with acetic anhydride in 81% yield, and converted to the acid chloride by treatment with thionyl chloride. The subsequent steps were the following: reaction with diazomethane to give the diazomethyl ketone (90% yield), which with hydrogen chloride yielded the chloromethyl ketone (86%); Meerwein–Pondorff reduction to the chlorohydrin (isolated in 80% yield as the 8-hydroxy compound after hydrolysis of the acetoxy group), followed by coupling with secondary amines to give III (32–45%). IIIa, b and c were isolated by crystallization from methanol and moist ether as pale yellow dihydrochloride sesquihydrates. The salts obtained by crystallization from anhydrous solvents absorbed water rapidly from the air, giving the sesquihydrates. Analytically pure anhydrous salts were not obtained, for the sesquihydrates lost some hydrogen chloride in addition to water on drying at 65–70° and 20 mm. pressure. Several attempts to replace the 8-hydroxyl group in IIIb with the amino or 4-diethylamino-1-methylbutylamino (novalamino) group through the Bucherer reaction were unsuccessful, as was the case in the 2-phenyl series.[2]

When the synthesis of 8-amino-2-phenyl King-Work types (I) was accomplished from 8-nitro-2-phenylcinchoninic acid,[2] a similar method was adopted in the present investigation. 6-Methoxy-8-nitrolepidine was chosen as the starting material rather than 8-nitrolepidine because it was readily available, and the 6-methoxy group in the final drugs (II) would be expected to increase their antimalarial activity as 8-aminoquinolines. A satisfactory conversion of 6-methoxy-8-nitrolepidine to 6-methoxy-8-nitrocinchoninic acid was accomplished by oxidation with selenium dioxide in a mixture of chlorobenzene and acetic acid, followed by oxidation of the crude aldehyde with potassium permanganate in aqueous pyridine. By this method 6-methoxy-8-nitrocinchoninic acid, m. p. 259–260° (dec.), was obtained in 70% yield. The acid forms a hemihydrate which slowly loses its water of crystallization at 140°.[3] The acid was converted to diazomethyl (6-methoxy-8-nitro-4-quinolyl) ketone in 97% yield through reaction of the acid chloride with diazomethane. The diazomethyl ketone and hydrogen chloride yielded chloromethyl (6-methoxy-8-nitro-4-quinolyl) ketone as a very insoluble hydrochloride, which was converted to the base (isolated in 80% yield) by repeatedly extracting with hot chloroform and treating the extracts with dilute sodium bicarbonate solution. Reduction of the chloromethyl ketone with aluminum isopropoxide yielded the chlorohydrin (84%), which was coupled with

(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 the Massachusetts Institute of Technology.

(2) Turner and Cope, THIS JOURNAL, **68**, 2214 (1946).

(3) British Patent 388,087 (1932) states that 6-methoxy-8-nitrocinchoninic acid may be prepared from *p*-methoxy-*o*-nitroformanilide and pyruvic acid, and gives its m. p. as 170° (dec.). We were unable to repeat this preparation, and observed an entirely different m. p. for the acid obtained by another method as noted above. The same patent describes 6-methoxy-8-nitrolepidine (obtained from *p*-methoxy-*o*-nitroformanilide and acetone) as a white solid which does not melt below 250°, while others have found it to be a yellow compound melting at 171–172° (see ref. 9).

diethylamine, di-*n*-butylamine and di-*n*-hexylamine to give the α-(dialkylaminomethyl)-6-methoxy-8-nitro-4-quinolinemethanols (16–52%). Hydrogenation in ethyl acetate or methanol solution in the presence of Adams platinum catalyst gave IIa, b and c. Only IIa was isolated as a crystalline base, which was converted to a dihydrochloride monohydrate for pharmacological testing. IIb was isolated as the dihydrochloride hemihydrate, and IIc as an anhydrous dihydrochloride.

Compounds IIa, b, c and IIIa, b, c were tested for antimalarial activity in avian malaria. Only IIb showed activity at the dose levels which were tested. The data are summarized in Table I.[4]

TABLE I

AVIAN ANTIMALARIAL ACTIVITIES

Cpd.	Code no.	Quinine equiv. (lophurae in the duck)	Test
IIa	MIT-50	$Q < 0.25$	G-5
IIb	MIT-51	Q[a]	G-5
IIc	MIT-52	$Q < 0.2$	G-5
IIIa	MIT-47	$Q < 0.25$	D-1
IIIb	MIT-48	$Q < 0.125$	D-1
IIIc	MIT-49	$Q < 0.5$	D-1

[a] Slight activity but not greater than Q 0.2.

Experimental[5]

8-Acetoxycinchoninic Acid.—Cinchoninic acid was sulfonated and the resulting 8-sulfocinchoninic acid was converted to 8-hydroxycinchoninic acid by alkali fusion according to a procedure developed by Gilman and Tolman.[6] Fifty grams of 8-hydroxycinchoninic acid was dissolved in a solution of 48 g. of sodium hydroxide in 250 ml. of water and acetic anhydride (35 g.) was added to the solution with vigorous stirring. The mixture was allowed to stand for twenty minutes. After acidification to a *p*H of 3 with dilute hydrochloric acid, the product was filtered, washed several times with water and dried at 110°. Four grams of 8-hydroxycinchoninic acid was recovered from the filtrate after standing for several days. The crude product, m. p. 215–216.5°, weighed 54 g. After treatment with decolorizing charcoal and two recrystallizations from dioxane 49 g. (81%) of 8-acetoxycinchoninic acid was obtained, m. p. 220–220.5°.

Anal. Calcd. for $C_{12}H_9O_4N$: C, 62.33; H, 3.92; N, 6.06. Found: C, 62.36; H, 4.00; N, 6.04.

Diazomethyl-(8-acetoxy-4-quinolyl) Ketone.—8-Acetoxycinchoninic acid (16.5 g., 0.0715 mole) was suspended in 200 ml. of dry benzene and 50 ml. of redistilled thionyl chloride was added. The mixture was refluxed for four and one-half hours, after which time all of the material was in solution. The solvents were removed under reduced pressure and the residue was dissolved in dry benzene and again distilled to dryness under reduced pressure. This process was repeated three times to remove the last traces of thionyl chloride. The crude acid chloride was dissolved in 150 ml. of dry benzene and added slowly to an ice-cold solution of 0.146 mole of diazomethane in 470 ml. of ether, previously dried over potassium hydroxide.[7] After standing overnight at 5°, the solvents were removed under reduced pressure and the product was washed onto a filter with ether. The yield of product melting at 120–121.5° (dec.) was 16.3 g. (90%). A sample was purified for analysis by four recrystallizations from methylene chloride–petroleum ether; m. p. 121.5–122° (dec.).

Anal. Calcd. for $C_{13}H_9O_3N_3$: C, 61.18; H, 3.56; N 16.5. Found: C, 61.17; H, 3.72; N, 16.3.

Chloromethyl-(8-acetoxy-4-quinolyl) Ketone.—A solution of 13.7 g. of the above diazomethyl ketone in 300 ml. of methylene chloride was saturated with dry hydrogen chloride at 0°. Acetyl chloride (15 ml.) was added to prevent any hydrolysis of the acetoxy group by traces of water and the solution was allowed to stand overnight at room temperature. Some quantity of the product separated as a hydrochloride on standing. The mixture was distilled to dryness under reduced pressure to remove acetyl chloride, and the residue was shaken with methylene chloride and dilute sodium bicarbonate solution to convert the hydrochloride to the free base. The methylene chloride layer was washed with saturated sodium chloride solution, filtered through anhydrous sodium sulfate, concentrated and diluted with petroleum ether. The crystalline product was obtained in two crops: 10.0 g., m. p. 138–139.5°, and 2.1 g., m. p. 137.5–139.5° (crude yield 86%). An analytical sample which was recrystallized four times from methylene chloride–petroleum ether melted at 140–140.5°.

Anal. Calcd. for $C_{13}H_{10}O_3NCl$: C, 59.35; H, 3.83; N, 5.33; Cl, 13.5. Found: C, 59.37; H, 3.95; N, 5.42; Cl, 13.5.

Chloromethyl-(8-hydroxy-4-quinolyl) Ketone.—A 0.25-g. sample of chloromethyl (8-acetoxy-4-quinolyl) ketone was dissolved in chloroform and treated with a large excess of methanolic hydrogen chloride. After standing overnight at room temperature, water was added, and the chloroform layer was separated. After washing with dilute sodium bicarbonate solution, saturated sodium chloride solution and filtering through anhydrous sodium sulfate, the chloroform solution was concentrated and the residue crystallized twice from ethanol. The product melted at 132–133°.

Anal. Calcd. for $C_{11}H_8O_2NCl$: C, 59.61; H, 3.64; N, 6.32; Cl, 16.0. Found: C, 59.44; H, 3.73; N, 6.20; Cl, 16.1.

α-(Chloromethyl)-8-hydroxy-4-quinolinemethanol.—A solution of 11.2 g. (0.0426 mole) of chloromethyl (8-acetoxy-4-quinolyl) ketone in 200 ml. of dry isopropyl alcohol to which 95 ml. of 0.9 molar aluminum *i*-propoxide in *i*-propyl alcohol had been added was distilled slowly through a 38-cm. Vigreux column for thirty-five minutes, after which time negative tests for acetone were obtained on the distillate. Slow distillation was continued for one hour, after which most of the solvent was removed under reduced pressure. A mixture of 200 ml. of concd. hydrochloric acid and 100 ml. of ethanol was added, and the resulting solution was warmed on the steam-bath for one-half hour to complete hydrolysis of the 8-acetoxy group. The solution was concentrated to dryness under reduced pressure, and the residue was washed with 200 ml. of water in four portions to remove aluminum salts. The residual hydrochloride was converted to the free base by shaking with chloroform and dilute sodium bicarbonate solution. The chloroform layer was washed with a saturated solution of sodium chloride, filtered through anhydrous sodium sulfate and concentrated under reduced pressure. Crystallization from ethanol–cyclohexane gave the product in two crops: 6.60 g., m. p. 142–143°, and 1.05 g., m. p. 139–141° (crude yield 80%). An analytical sample which was recrystallized four times from ethanol–cyclohexane melted at 142–143°.

(4) These results were obtained too late for inclusion in a forthcoming monograph prepared by the Survey of Antimalarial Drugs and are reported in this paper at the suggestion of Dr. E. K. Marshall, Jr. We are indebted to Dr. Marshall for the D-1 tests and to Dr. Arthur P. Richardson for the tests by procedure G-5. Both procedures will be described in the monograph. Dr. Marshall and Dr. Richardson state that the two procedures give comparable results.

(5) All melting points are corrected.

(6) Gilman and Tolman, THIS JOURNAL, in press. Fuson, *ibid.*, **47**, 2018 (1925), used the same sequence of reactions in a smaller scale preparation in which the sulfonation was carried out in a sealed tube.

(7) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, New York, N. Y., 1943, p. 165.

Anal. Calcd. for $C_{11}H_{10}O_2NCl$: C, 59.07; H, 4.51; N, 6.26; Cl, 15.9. Found: C, 59.12; H, 4.51; N, 6.29; Cl, 15.8.

α-(Diethylaminomethyl)-8-hydroxy-4-quinolinemethanol Dihydrochloride Sesquihydrate (IIIa, MIT-47).—A mixture of 2.24 g. of α-(chloromethyl)-8-hydroxy-4-quinolinemethanol and 25 ml. of diethylamine was sealed in a bomb tube and shaken in an electrically heated jacket at 110° for fifteen hours. The contents of the tube were poured into ether and the diethylamine hydrochloride which had separated was removed by filtration. The filtrate was concentrated under reduced pressure, and the residue was taken up in benzene and again distilled to dryness to remove traces of diethylamine. The residual oil was dissolved in an excess of methanolic hydrogen chloride, which was then diluted with ether. The product was recrystallized twice from methanol and moist ether, and was obtained as light yellow crystals (yield 1.62 g., 45%) which melted at 153–154°, solidified and remelted at 235–239° (dec.) with gradual decomposition beginning at 210°.[8]

Anal. Calcd. for $C_{15}H_{20}O_2N_2 \cdot 2HCl \cdot 1^1/_2H_2O$: C, 50.00; H, 7.00; N, 7.78; Cl, 19.7. Found: C, 50.24; H, 7.08; N, 7.99; Cl, 19.5.

α-(Diethylaminomethyl)-8-hydroxy-4-quinolinemethanol.—An aqueous solution of a small amount of the above dihydrochloride sesquihydrate was made alkaline with sodium bicarbonate and extracted with ether. The ether extracts were combined, dried and concentrated, and the residue was purified by several recrystallizations from cyclohexane; m. p. 86–86.5°.

Anal. Calcd. for $C_{15}H_{20}O_2N_2$: C, 69.20; H, 7.74; N, 10.8. Found: C, 69.40; H, 7.87; N, 10.8.

α-(Di-*n*-butylaminomethyl)-8-hydroxy-4-quinolinemethanol Dihydrochloride Sesquihydrate (IIIb, MIT-48).—A mixture of 2.24 g. of α-(chloromethyl)-8-hydroxy-4-quinolinemethanol and 10 ml. of di-*n*-butylamine was heated in an oil-bath at 130–135° for four hours. The mixture was cooled, diluted with ether, and filtered to remove dibutylamine hydrochloride. The filtrate was steam distilled until the odor of dibutylamine had disappeared. The oily residue was dissolved in ether, washed with saturated sodium chloride solution, filtered through anhydrous sodium sulfate, and concentrated. The residue was dissolved in methanol, acidified with hydrogen chloride, and the solution was diluted with moist ether. The product was recrystallized twice from methanol and moist ether; yield 1.70 g. (40%), m. p. 128–130°. The melt solidified and remelted at 230–232° (dec.) with gradual decomposition above 220°.

Anal. Calcd. for $C_{19}H_{28}O_2N_2 \cdot 2HCl \cdot 1^1/_2H_2O$: C, 54.80; H, 7.99; N, 6.73; Cl, 17.0. Found: C, 54.61; H, 8.15; N, 6.77; Cl, 16.9.

A small sample of the salt was converted to the free base by the method described above. After several crystallizations from petroleum ether it melted at 65–65.5°.

Anal. Calcd. for $C_{19}H_{28}O_2N_2$: C, 72.11; H, 8.92; N, 8.86. Found: C, 72.06; H, 9.12; N, 8.90.

α-(Di-*n*-hexylaminomethyl)-8-hydroxy-4-quinolinemethanol Dihydrochloride Sesquihydrate (IIIc, MIT-49).—A mixture of α-(chloromethyl)-8-hydroxy-4-quinolinemethanol (6.00 g.) and di-*n*-hexylamine (60 g.) was heated in an oil-bath at 130° for four hours. The mixture was diluted with chloroform, washed with sodium bicarbonate solution, and steam distilled to remove dihexylamine. The product was isolated by the procedure described above and purified by three crystallizations from methanol and moist ether. A yield of 4.10 g. (32%) was obtained of material which melted at 131–132°, solidified and remelted at 225–227° (dec.) with gradual decomposition above 215°.

Anal. Calcd. for $C_{23}H_{36}O_2N_2 \cdot 2HCl \cdot 1^1/_2H_2O$: C, 58.46; H, 8.75; N, 5.93; Cl, 15.0. Found: C, 58.32; H, 8.99; N, 6.08; Cl, 15.0.

The corresponding free base failed to crystallize.

6-Methoxy-8-nitrocinchoninic Acid.—6-Methoxy-8-nitrolepidine[9] (60.0 g., 0.275 mole) was dissolved in 400 ml. of chlorobenzene and 100 ml. of glacial acetic acid[10] and 46.0 g. (0.414 mole) of selenium dioxide was added. The mixture was boiled under reflux for forty-eight hours, filtered to remove selenium and concentrated under reduced pressure. The residue was dissolved in 800 ml. of pyridine, and a solution of 40.0 g. of potassium permanganate in 800 ml. of water was added slowly while the temperature of the mixture was kept below 40°. Although this quantity of potassium permanganate was in excess of the amount required to convert the aldehyde to the corresponding acid, the permanganate color was discharged on standing overnight. This result presumably was due to the presence of oxidizable by-products formed in the selenium dioxide oxidation. The precipitated manganese dioxide was removed by filtration and washed with five 100-ml. portions of hot water. The filtrate and washings were combined and taken to dryness under reduced pressure to remove the pyridine. The residue was dissolved in water by adding a small amount of potassium hydroxide and acidified with acetic acid. The crude product was separated by filtration, crystallized from dilute dioxane, and dried in an oven at 140°; yield 47.8 g. (70%), m. p. 258–259° (dec.). An analytical sample was recrystallized three times from dilute dioxane and dried at 140° and 20 mm.; m. p. 259–260° (dec.).

Anal. Calcd. for $C_{11}H_8O_5N_2$: C, 53.23; H, 3.25; N, 11.39. Found: C, 53.16; H, 3.35; N, 11.5.

An analytical sample which was air-dried at room temperature had the same melting point but was shown by analysis to be the hemihydrate.

Anal. Calcd. for $C_{11}H_8O_5N_2 \cdot 1/_2H_2O$: C, 51.37; H, 3.53; N, 10.9; H_2O, 3.5. Found: C, 51.40; H, 3.69; N, 11.0; H_2O (by loss in weight on drying), 3.5.

The methyl ester was prepared from the acid by treatment with diazomethane. After crystallization from chloroform–petroleum ether it melted at 171–172°.

Anal. Calcd. for $C_{12}H_{10}O_5N_2$: C, 54.96; H, 3.84; N, 10.7. Found: C, 54.98; H, 4.08; N, 10.9.

Diazomethyl (6-Methoxy-8-nitro-4-quinolyl) Ketone.—A suspension of 47.0 g. (0.190 mole) of 6-methoxy-8-nitrocinchoninic acid in 600 ml. of dry benzene and 200 ml. of thionyl chloride was refluxed for four and one-half hours, after which time all of the material was in solution. The solution was concentrated under reduced pressure and taken to dryness four times after addition of benzene to remove traces of thionyl chloride. The crude acid chloride was dissolved in 1 liter of dry benzene and added slowly to an ice-cold solution of 0.450 mole of diazomethane in 1.5 l. of ether which previously had been dried over potassium hydroxide for three hours. After standing overnight at 5° the ether suspension was taken to dryness under reduced pressure, and the crude product was washed onto a filter with ether; yield 49.9 g. (97%), m. p. 168–170° (dec.). A sample purified by three recrystallizations from methylene chloride–petroleum ether melted at 170–171° (dec.).

Anal. Calcd. for $C_{12}H_8O_4N_4$: C, 52.94; H, 2.96; N, 20.6. Found: C, 52.91; H, 3.12; N, 20.3.

Chloromethyl-(6-methoxy-8-nitro-4-quinolyl) Ketone.—A solution of 49.5 g. of the crude diazomethyl ketone described above in 2 liters of methylene chloride was saturated with dry hydrogen chloride. Nitrogen was evolved rapidly and a crystalline precipitate soon appeared. After standing overnight the solvent was removed under reduced pressure and the residue was extracted repeatedly

(8) When crystallized from dry methanol and ether the product was erratic in m. p. and slowly took up moisture from the air to give the sesquihydrate.

(9) Prepared by the method of Campbell, Sommers, Kerwin and Campbell, THIS JOURNAL, **68**, 1558 (1946); m. p. 171–172°.

(10) This solvent has been employed for selenium dioxide oxidations by McKenzie, Engel, Mattox and Kendall, *J. Biol. Chem.*, in press.

with hot chloroform until all of it had been dissolved. The extracts were shaken with sodium bicarbonate solution to liberate the free base. The chloroform solution of the base was then washed with saturated sodium chloride solution, filtered through anhydrous sodium sulfate, and concentrated until the product began to crystallize. It was obtained in two crops: 36.3 g., m. p. 191–192°, and 4.6 g., m. p. 189–190° (total crude yield 80%). An analytical sample which was crystallized three times from chloroform melted at 193.5–194.5°.

Anal. Calcd. for $C_{12}H_9O_4N_2Cl$: C, 51.35; H, 3.23; N, 9.98; Cl, 12.6. Found: C, 51.58; H, 3.24; N, 10.1; Cl, 12.6.

α-(Chloromethyl)-6-methoxy-8-nitro-4-quinolinemethanol.—A mixture of 38.0 g. (0.135 mole) of the above crude chloromethyl ketone, 1 liter of dry isopropyl alcohol and 180 ml. of 1 molar aluminum *i*-propoxide in *i*-propyl alcohol was distilled slowly through a 38-cm. Vigreux column. The quite insoluble ketone soon dissolved, and negative tests for acetone in the distillate were obtained after forty minutes. The distillation was continued for a total time of one and one-half hours, after which the remaining isopropyl alcohol was removed under reduced pressure. Water was added to the residue and the suspension of the product and aluminum hydroxide was extracted with chloroform until no further color was removed. The extracts were combined, washed with water and saturated sodium chloride solution, and dried over anhydrous sodium sulfate. Concentration and dilution with petroleum ether gave 32.0 g. (84%) of a product melting at 133–134°. Three recrystallizations from chloroform–petroleum ether did not alter the melting point of the sample purified for analysis.

Anal. Calcd. for $C_{12}H_{11}O_4N_2Cl$: C, 50.98; H, 3.92; N, 9.91; Cl, 12.5. Found: C, 50.84; H, 4.05; N, 9.84; Cl, 12.7.

α-(Diethylaminomethyl)-6-methoxy-8-nitro-4-quinolinemethanol.—A mixture of 10.0 g. of the above chlorohydrin and 40 ml. of diethylamine was heated in a sealed tube at 110° and shaken for fourteen hours. The mixture was diluted with ether, filtered to remove diethylamine hydrochloride and concentrated under reduced pressure. The residue was taken up in benzene, again distilled to dryness to remove diethylamine, and the residual oil was triturated with several portions of hot cyclohexane. The tarry residue was discarded and the extracts were combined, treated with Darco (decolorizing charcoal), and cooled. The solid product was recrystallized twice from methanol; yield 5.80 g. (52%), m. p. 107–108°. An analytical sample recrystallized two more times from methanol had the same melting point.

Anal. Calcd. for $C_{16}H_{21}O_4N_3$: C, 60.17; H, 6.63; N, 13.2. Found: C, 60.29; H, 6.82; N, 13.1.

α-(Diethylaminomethyl)-8-amino-6-methoxy-4-quinolinemethanol (IIa, MIT-50).—The above nitro compound (5.00 g.) in 30 ml. of ethyl acetate was hydrogenated in the presence of 0.35 g. of pre-reduced platinum oxide catalyst. Three molar equivalents of hydrogen were absorbed in forty minutes. The product was crystallized from ether–petroleum ether; yield 4.14 g. (90%), m. p. 74–75°. An analytical sample which was recrystallized twice from ether–petroleum ether melted at 75–76°.

Anal. Calcd. for $C_{16}H_{23}O_2N_3$: C, 66.41; H, 8.01; N, 14.5. Found: C, 66.34; H, 8.15; N, 14.4.

The above base (3.60 g.) was dissolved in an excess of hot methanolic hydrogen chloride. The orange product which separated on cooling (4.25 g., 92%) melted at 207–208° (dec.) after equilibration in air. An analytical sample which was recrystallized twice from methanol and air dried had the same melting point.

Anal. Calcd. for $C_{16}H_{23}O_2N_3 \cdot 2HCl\ H_2O$: C, 50.53; H, 7.16; N, 11.1; Cl, 18.7; H_2O, 4.73. Found: C, 50.48; H, 7.28; N, 11.1; Cl, 18.7; H_2O (by loss in weight), 4.63.

A sample of the hydrate which was dehydrated at 150° and 20 mm. did not change in melting point.

Anal. Calcd. for $C_{16}H_{23}O_2N_3 \cdot 2HCl$: C, 53.04; H, 6.96; N, 11.6; Cl, 19.6. Found: C, 53.25; H, 7.02; N, 11.7; Cl, 19.5.

α-(Di-*n*-butylaminomethyl)-6-methoxy-8-nitro-4-quinolinemethanol.—A mixture of 10.0 g. of α-(chloromethyl)-6-methoxy-8-nitro-4-quinolinemethanol and 50 ml. of di-*n*-butylamine was heated in a bath at 130° for three and one-half hours. The mixture was diluted with ether, filtered to remove dibutylamine hydrochloride, and steam distilled until the odor of dibutylamine disappeared. The residue was taken up in ether, washed with saturated sodium chloride solution, filtered through anhydrous sodium sulfate, and concentrated. The residual oil was triturated with several portions of hot petroleum ether (b. p. 58–86°). The extracts were combined, treated with Darco and concentrated to a small volume. The crude solid was recrystallized twice from methanol. The yield of the nearly white product, m. p. 73–74.5°, was 3.58 g. (27%). An analytical sample purified by recrystallization from methanol and dilute methanol melted at 75–75.5°.

Anal. Calcd. for $C_{20}H_{29}O_4N_3$: C, 63.98; H, 7.79; N, 11.2. Found: C, 64.10; H, 7.93; N, 11.4.

α-(Di-*n*-butylaminomethyl)-8-amino-6-methoxy-4-quinolinemethanol Dihydrochloride Hemihydrate (IIb, MIT-51).—The above nitro compound (2.70 g.) in 25 ml. of methanol was hydrogenated in the presence of 0.15 g. of pre-reduced platinum oxide catalyst during thirty-five minutes. After removal of the solvent a yellow oil remained which failed to crystallize. It was dissolved in an excess of methanolic hydrogen chloride and the solution was diluted with ether. The solid which separated on standing was recrystallized from methanol–ether. The yield of a product which gradually darkened beginning at 190°, sintered at 215–217°, and did not melt below 300° was 2.57 g. (84%). An analytical sample which was recrystallized twice from methanol–ether sintered at the same temperature.

Anal. Calcd. for $C_{20}H_{31}O_2N_3 \cdot 2HCl \cdot {}^1/_2H_2O$: C, 56.20; H, 8.02; N, 9.83; Cl, 16.6; H_2O, 2.11. Found: C, 56.23; H, 8.05; N, 9.80; Cl, 16.7; H_2O (by loss in weight on drying), 2.02.

The anhydrous salt was obtained by drying to constant weight at 100° and 20 mm. This salt showed similar characteristics to the above hemihydrate when heated. Sintering at 215° was less pronounced.

Anal. Calcd. for $C_{20}H_{31}O_2N_3 \cdot 2HCl$: C, 57.41; H, 7.95; N, 10.0; Cl, 17.0. Found: C, 57.44; H, 8.02; N, 10.0; Cl, 17.0.

α-(Di-*n*-hexylaminomethyl)-6-methoxy-8-nitro-4-quinolinemethanol.—α-(Chloromethyl)-6-methoxy-8-nitro-4-quinolinemethanol (10.0 g.) and 40 ml. of di-*n*-hexylamine were heated together in a bath at 130–135° for four and one-half hours. The product was isolated in approximately the same manner as the corresponding di-*n*-butylamino compound. The crude solid which crystallized from the concentrated petroleum ether extracts was recrystallized twice from petroleum ether and once from methanol, and yielded 2.42 g. (16%) of a product melting at 95–97°. An analytical sample which was recrystallized four times from methanol melted at 99–99.5°.

Anal. Calcd. for $C_{24}H_{37}O_4N_3$: C, 66.79; H, 8.64; N, 9.74. Found: C, 67.01; H, 8.72; N, 9.66.

α-(Di-*n*-hexylaminomethyl)-8-amino-6-methoxy-4-quinolinemethanol Dihydrochloride (IIc, MIT-52).—The above nitro compound (1.95 g.) was dissolved in 25 ml. of ethyl acetate and hydrogenated in the presence of 0.15 g. of pre-reduced platinum oxide during one hour. The yellow oil which remained after removing the solvent was converted to the dihydrochloride by dissolving it in an excess of methanolic hydrogen chloride. After ether was added the salt crystallized; yield 1.86 g. (87%), m. p. 198–199° (dec.). An analytical sample which was recrystallized twice from methanol–ether had the same m. p.

Anal. Calcd. for $C_{24}H_{39}O_2N_3 \cdot 2HCl$: C, 60.75; H, 8.71; N, 8.86; Cl, 15.0. Found: C, 60.59; H, 8.99; N, 8.73; Cl, 15.0.

Acknowledgment.—We are indebted to Mr. S. M. Nagy for all analyses.

Summary

The syntheses of three α-(dialkylaminomethyl)-8-amino-6-methoxy-4-quinolinemethanols (IIa, b, c) and three α-(dialkylaminomethyl)-8-hydroxy-4-quinolinemethanols (IIIa, b, c) are described. These compounds have been tested for avian antimalarial activity.

CAMBRIDGE, MASSACHUSETTS RECEIVED JUNE 25, 1946

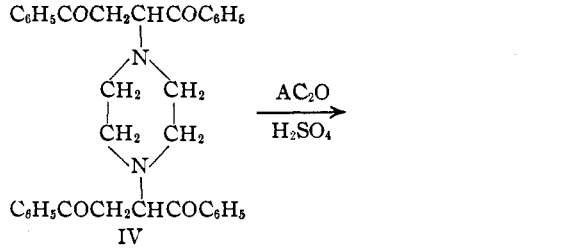
[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

Some α-*t*-Amino-*s*-dibenzoylethanes and 3-*t*-Amino-2,5-diphenylfurans. The Preparation and Reactions of Dibenzoyl-N-morpholinoethylene[1]

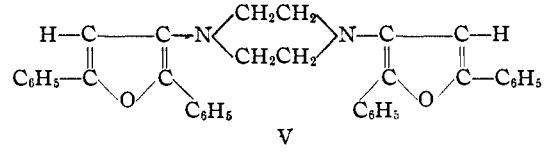
BY ROBERT E. LUTZ, PHILIP S. BAILEY[2a] AND NEWTON H. SHEARER, JR.[2]

In an earlier paper the unexpected results obtained in the reaction between amines and dibenzoylmethylethylene were described.[3] The present communication deals with the straightforward addition of amines to *trans*-dibenzoylethylene (I) to give α-aminodibenzoylethanes (II) and with the reactions of the products. A number of these compounds were made in connection with the search for new types of antimalarials.

In 1900 Paal and Schulze[4] added aniline to both *cis*- and *trans*-dibenzoylethylene by warming a mixture of the reactants. In the present work the analogous additions of a number of aliphatic amines were carried out at room temperature either in ether or in ethanol solution. The amines used were dimethylamine, diethylamine, morpholine; piperidine, piperazine, 1-amylpiperazine and 1-benzylpiperazine.

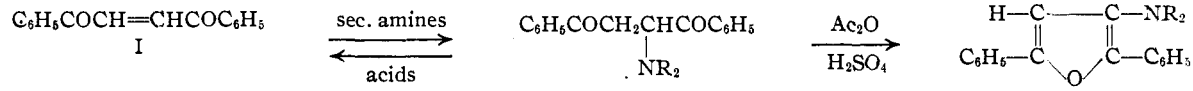


IV



V

The hypothetical monoaddition compound, dibenzoyl-N-piperazinoethane, could not be isolated, even when a three molal excess of piperazine was used. A likely explanation for the failure to obtain it is found in the general instability of these addition compounds and in the comparatively high insolubility of the piperazino-*bis*-dibenzoylethane (IV). Probably the mono additive is formed in equilibrium with the components, with the *bis* compound the only product isolated because of its insolubility.



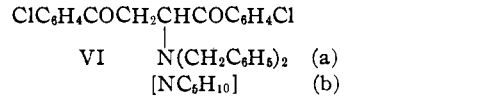
II (a) $NR_2 = N(CH_3)_2$
(b) $NR_2 = N(C_2H_5)_2$
(c) NR_2 = morpholino
(d) NR_2 = piperidino
(e) $NR_2 = H{<}C_4H_8{>}NC_5H_{11}$[4a]
(f) $NR_2 = N{<}C_4H_8{>}NCH_2C_6H_5$[4a]

III (c) NR_2 = morpholino
(d) NR_2 = piperidino
(f) $NR_2 = N{<}C_4H_8{>}NCH_2C_6H_5$[4a]

Only one of these products had been made before, namely, dibenzoyldimethylaminoethane (IIa) by rearrangement of diphenacyldimethylammonium bromide by means of alkali.[5]

In the case of the piperazine addition the *bis*-compound (IV) was formed, as would be expected, by the reaction of two molecules of dibenzoylethylene (I) with one of piperazine.

Along with the compounds described above N,N-dibenzylamino and N-piperidino-di-(*p*-chlorobenzoyl)-ethane (VIa and b) were obtained by the addition of the appropriate amines to di-(*p*-chlorobenzoyl)-ethylene. These compounds were made for antimalarial testing with a view toward the possible activating influence of the two para chlorines.



VI (a) $N(CH_2C_6H_5)_2$
(b) $[NC_5H_{10}]$

(1) Part of 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 the University of Virginia. The Survey Number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activities of these compounds to which Survey Numbers have been assigned will be tabulated in a forthcoming monograph.

(2) (a) Holder of Philip Francis du Pont Fellowship, 1942–1944; present address: University of Texas, Austin, Texas. (b) Present address: Tennessee Eastman Corporation, Kingsport, Tennessee.

(3) Lutz and Bailey, THIS JOURNAL, **67**, 2229 (1945).

(4) Paal and Schulze, *Ber.*, **33**, 3795 (1900).

(4a) [—N<C₄H₈>N—] is the piperazine nucleus.

(5) Thomson and Stevens, *J. Chem. Soc.*, 1932 (1932).